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Moffett Field, California
January 30-31, 1978

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Space Gerontology

Edited by
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Moffett Field, California

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Mountain View, California

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National Aeronautics
and Space Administration

**Scientific and Technical
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WORKSHOP PROCEEDINGS

STEPS TOWARD SPACE GERONTOLOGY

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Moffett Field, California
on January 30-31, 1978

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PREFACE

A recent report of the National Academy of Sciences on biological research in space stresses that "an ongoing organic relationship between the NASA life scientists and life scientists working in universities, institutes, and medical schools seems essential." Further, the report notes that the partnership should begin with problem statement and should continue with the experimental design.

This publication deals with an effort to implement the above guidelines in the specific area of research on fundamental mechanisms of aging as influenced by weightlessness.

Preliminary USA and USSR experiments suggest that the aging process of insects exposed to the space environment on board biosatellites may be influenced by zero gravity. Moreover, some effects of long-duration space flights on cosmonauts and astronauts, such as muscle atrophy and bone demineralization, support the concept that some organ systems may show accelerated senescence in weightlessness. At a more fundamental level, because the normal aging process evolved under conditions of constant gravity, removal of this environmental factor (with concomitant metabolic and neuroendocrine alterations) may result in a change in the general rate of organismic aging. The expected results would considerably interest experimental gerontologists concerned with the intricate relationships between metabolic rate, neuroendocrine clocks, and senescence.

A question of both theoretical and practical interest is the influence of age on adaptation of experimental animals and human subjects to zero-g.

In view of the above, the Editors of these Proceedings were pleased that their interest in studies of aging at zero-g was shared by eminent gerontologists from the National Institute on Aging and from other institutes and universities. Thus, a workshop was planned and structured to encourage the free exchange of ideas and productive interaction between NASA scientists interested in the possible gerontological relevance of their experiments and gerontologists intrigued by the possibility of studying aging in the absence of gravity.

We feel that this meeting was very effective in establishing a working partnership between the NASA and the non-NASA scientists. In our opinion, considerable progress was made towards defining the goals of space gerontology and discussing concrete experiments compatible with the engineering constraints of the Shuttle Space Transportation System.

These proceedings are a compilation of the Workshop presentations and discussions. Several articles dealing with related subjects are also included as appendices.

The Editors thank Dr. H. P. Klein, Dr. A. Comfort, and all the other participants in the Workshop for their essential support.

Jaime Miquel and Angelos C. Economos
NASA Ames Research Center

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A FRAMEWORK FOR THE WORKSHOP

Harold P. Klein

Ames Research Center

I would like to spend a few minutes setting the background for you as to why NASA and the Ames Research Center, as a part of NASA, are supporting and sponsoring this conference. Why are we becoming interested in gerontology? I would like to make sure, as we initiate this meeting, that our guests understand this point.

You are probably all well aware of NASA's activities in lunar and planetary exploration. I think you recognize that, in the past and for the present, science within NASA has primarily involved physical research. The scientists that we have dealt with for the most part have been astronomers, geophysicists, planetologists, meteorologists, and geologists. We have always, however, had a life sciences capability within NASA. Approximately 1% of NASA's total manpower is devoted to life sciences, and about 1% of NASA's total budget is devoted to these activities. Where has this life sciences effort been concentrated? It has been mainly in support of manned spaceflight. Over the years most of this 1% has gone to supporting capabilities in space and probably will continue in this area for some time to come, as there are important biomedical and technological issues still to be resolved.

Now, in addition to this primary, practical function of life sciences, we have conducted, over the past 15-20 years, a small number of space experiments in which scientific biological questions were foremost. We have – especially in the early days of NASA – tried to probe whether or not any new biological phenomena might be uncovered by going into space. Primarily, we were interested in weightlessness, because all other environmental conditions encountered in spaceflight, except possibly cosmic radiation, could readily be investigated on Earth. As a result of these probings and utilizing a variety of organisms, we have found that there are no profound effects on most organisms. Not surprisingly, those organisms, such as higher plants, that depend strictly and very substantially on orientation clearly suffer certain disturbances in the orientation of their stems and leaves. With higher animal organisms, we again see that they become disoriented upon entering weightlessness. Other changes that may be more significant, especially upon prolonged exposure to weightlessness, are also seen, but the mechanisms involved are not clear. The issue that brings us together today is that just over the horizon, in a few years, we will have available within NASA a "workhorse" called the Shuttle. We will have available a system which will allow experiments of all kinds to be ferried into space. The shuttles will become operational sometime in the early 1980s; the plans are for the shuttle program to continue on this basis at least into the 1990s.

Now, what is happening within the NASA community of scientists, that is, among the astronomers, the geophysicists, the planetologists, and all those in other fields, is that the various groups that have been working with NASA over the years are beginning to "stake out their claims" for space on these shuttles and for the resources to perform their experiments on board. Needless to say, we expect that some fraction of these payloads will be devoted to the life sciences. What we are doing now and, hopefully, what this meeting will contribute, is to so order the life sciences' priorities, that we can determine which types of life sciences' experiments would be the most important, the most interesting, and the most useful to be performed in the shuttles. We also hope that by listening to the interplay between you and our own

people we will be able to estimate the depth of your feelings and gauge the strength available to push forward into this type of biological research. There is no question that the shuttles will be investigating astronomy, because certain types of astronomical research are available above the clouds to a greater extent than can be studied from Earth. There is no question that looking down at Earth from the shuttle will allow us to study various global sciences in ways that aren't feasible from the ground. Possibly, the shuttle will be used to investigate the feasibility of carrying out certain kinds of manufacturing in a weightless environment. However, the question we are interested in is, "What is in it for the biologists?" We are asking this question of ourselves at NASA, and I hope you will keep this in mind as you meet for the next two days. Which important biological questions might be investigated by performing experiments in the zero-gravity environment of the shuttle? We will hear more in the program about these plans for the relatively comfortable and well-equipped spacelab that is to be carried aboard the shuttle. The initial flights will last anywhere from 7 to 30 days, according to current plans. If we are successful, this timespan will be increased, perhaps to a few months. Certainly in the beginning we will be talking about short-term experiments. The question becomes, then, how can we biologists best take advantage of the space environment?

This meeting is not the beginning of the biologists' attempts to assess the utility of doing shuttle experiments. In 1977, the National Academy of Sciences conducted a summer study to examine this at Snowmass, Colorado. Six panels of biologists spent approximately two weeks looking into these questions from the point of view of their specialties. No gerontologists were represented there. Emphasis was mainly on mammalian physiology, with one panel that addressed the question of cellular and plant physiology. These scientists looked at the outlines of the shuttle program; they are expected to give advice on areas in which to concentrate in planning shuttle experiments. Largely because of the persistence of Dr. Miquel over the last several months, and after a brief discussion with Dr. Comfort, I became convinced that perhaps we should informally constitute a "seventh" panel, so to speak. The idea was to look at biology from another aspect, a gerontological aspect, and it is in that context that I would like to see this meeting carry out its proceedings, almost as an addendum to the Snowmass meeting. The present meeting doesn't have the stamp of the National Academy, but I hope you will have equally important recommendations to make to NASA. From these, some experiments might materialize — or a program spanning several years — that will contribute to the field in which you are interested. A long-term commitment may well be necessary to accomplish significant achievements, and this should not discourage you. In previous spaceflight projects, NASA has often resorted to assembling science teams (groups of five to eight people) simply to plan for a particular mission or for a series of missions. To give you an example, on the Viking mission to Mars back in 1975, there were 14 such science teams. Each team represented a different branch of science, such as atmospheric science or biology. Some of the teams were put together back in the 1960s, well before the mission had been initiated. Each team had from six to ten years to plan for the experiments and to later implement these plans. I would be delighted if we could reach the point in this meeting to suggest the composition of such a team, if you feel strongly enough, because the best way to guarantee involvement in the shuttle program is to include people who become personally committed. If we could form a team willing to do some planning and then later take responsibility for devising the experiments, that would really be the best way to "stake out a claim" in this area. That is basically all I hoped to say to you. I wanted to give you my hopes for what should result from this meeting if there is to be gerontological research in space. Explore the concepts to decide if there is or is not research that the life sciences could proceed with and for which it would fight. We are not opposing the NIH; we are merely competing with other potential users of the Space Shuttle.

INTRODUCTORY REMARKS

Alex Comfort

Neuropsychiatric Institute, UCLA, Los Angeles, California

I would just like to say, ladies and gentlemen, that this is the first meeting of gerontologists and NASA experts. We want something you've got. You have the expertise to produce weightlessness over long periods of time and it does look to us as if this may prove to be a very important experimental tool in investigating the role of the hypothalamus in the senescence of animals and later in man. The model of aging that has always been popular in America, although I don't know why, maintained that there must be some overall fundamental process: either we run out of cell division or our DNA goes wrong or our collagen goes wrong. Gerontology has advanced along these lines, but more and more foxes are going to ground in the hypothalamus of the brain, and I think the model we are now perceiving is similar to that of a spaceship with components which all wear out. The space engineers choose tolerances to get the thing where it is going and while it is on its mission there is an in-flight computer which can switch in backup systems and modulate changes in the performance of the components. When the vehicle arrives at its destination, the computer switches off or loses interest or it may actually blow up the craft. We don't know which of these factors is true in the case of humans, but it is the "in-flight computer," the hypothalamus, which most of us here are interested in investigating. I would like to make it clear that we are not interested in ordinary space medicine in the sense of how you put astronauts in orbit and how you keep them well. We want the feedback the other way: what we can learn from the facilities you have that is likely to be of interest to this fundamental problem in gerontology and to other fundamental problems. I think all of this will prove extremely useful to us.

Historically, I was drawn to this problem by the possibility of using weightlessness as a tool to investigate the way in which body mass and food intake, which we believe modulate the rate of aging, would be affected by weightlessness. However, my interests are not, by any means, limited to this. Another important point is that when longer flights become possible, it will be worthwhile to notice the effects of differential organ growth likely to occur in animals developing at zero-g. Another question of both theoretical and practical interest is the influence of age on adaptation to spaceflight stresses including weightlessness, not only for mice and rats, but for human subjects as well. Because some day we may have aged scientists willing to go into space to perform experiments on board the Shuttle, we need to understand the response of old organisms to the stresses of spaceflight.

COMPARISON BETWEEN THE WEIGHTLESSNESS SYNDROME AND AGING

Jaime Miquel

Ames Research Center

Some preliminary experiments dealing with space gerontology have already been performed. In collaboration with Dr. Delbert E. Philpott (of this Center) and Dr. G. D. Parfenov (of the Institute of Biomedical Problems of Moscow), we have investigated the effects of space weightlessness on the development and aging process of Drosophila.

The experiments, which involved exposure of fruit flies to near zero-g for about 20 d in USSR biosatellites, suggest that the developmental process is not altered in weightlessness. On the other hand, flies that were exposed to weightlessness from the 7th to the 27th day of their adult lives showed a striking decrease in lifespan. Our tentative interpretation is that a weightlessness-induced increase in activity resulted in increased metabolic rate and concomitant shortening of life. Thus, the effects of weightlessness on Drosophila would be similar to those of relatively high ambient temperatures, which induce an increase in the rate of O_2 utilization and a decrease in lifespan (fig. 1).

Further research from our laboratory has revealed that fruit flies are very sensitive to altered environments, which, most likely, influence lifespan by their effect on metabolic rate and peroxidative disorganization of mitochondrial membranes. By contrast, homeotherms are endowed with a remarkable ability to preserve homeostasis in the face of environmental challenges. This, in our opinion, makes it difficult to predict what the probable effects of long-term exposure to weightlessness on the aging process of experimental mammals and human subjects will be.

In agreement with the basic concept of environmental gerontology illustrated by figure 2, any drastic deviation from the normal environment to which the species has adapted throughout its evolutionary history should be life-shortening and injurious to at least some organ systems. Thus, the detrimental effects of weightlessness on the musculo-skeletal system of rats, cosmonauts, and astronauts can be considered the unavoidable result of life in an abnormal environment. It is interesting with regard to the subject of this Workshop that these musculo-skeletal changes and other effects of zero-g summarized in table 1 are strikingly similar to the physiological alterations usually found in aging experimental animals and human subjects. Particularly, the muscle atrophy and calcium loss induced by exposure to zero-g are similar to atrophic changes occurring during human senescence (figs. 3-5, refs. 2-4).

It is generally accepted that the weightlessness-induced changes are fully reversible. However, it is very likely that exposure to zero-g for even longer periods than those of the longest spaceflights performed so far would induce irreversible alterations in skeletal muscle and in bone. This view is made plausible by the fact that the gastronecmius muscle of rats suffered irreversible pathological changes (including fat and collagen accumulation) after only 22 d of exposure to weightlessness in a USSR Kosmos flight (ref. 5). It is well known that the resistance of any organism to environmental stresses tends to decrease with age. Therefore, we suspect that the atrophy of muscles and bones would have been even more severe if middle-aged rats had been used by the USSR space biologists, instead of

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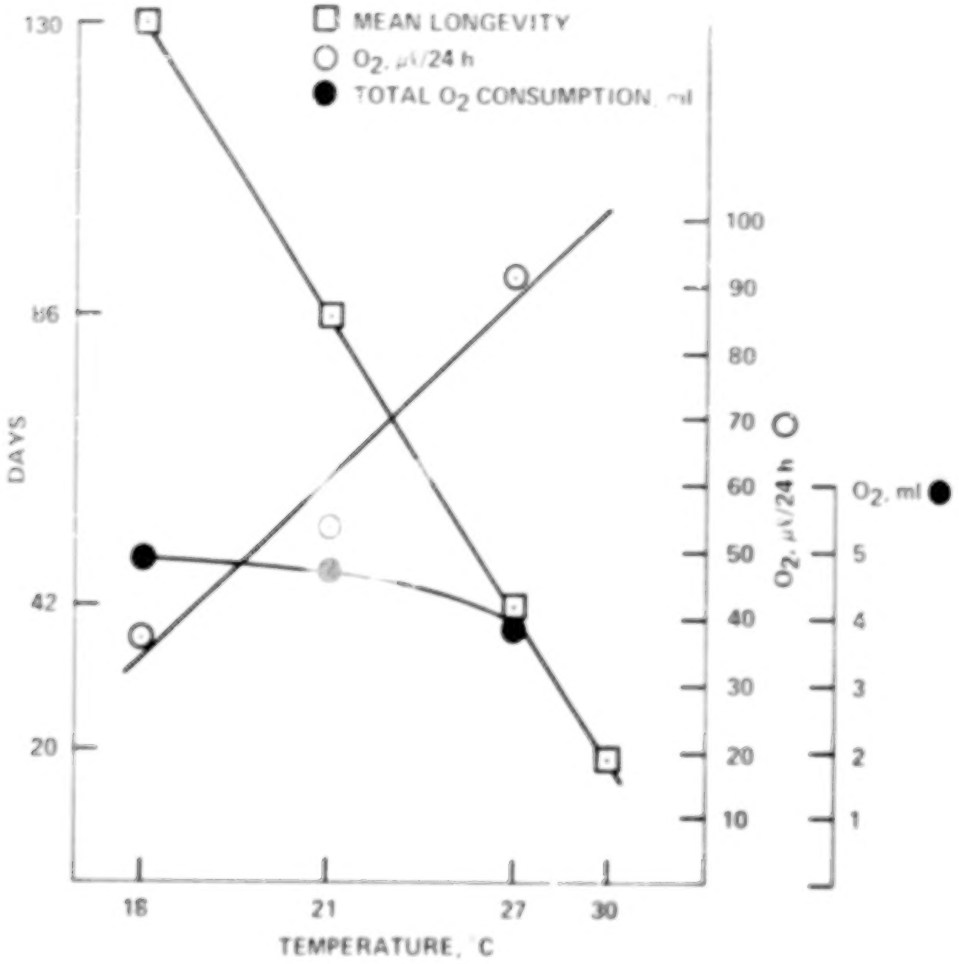

Figure 1.- Inverse relationship between mean longevity and O_2 utilization per male fruit fly in a 24-hr period. It is apparent that a male Drosophila melanogaster uses an almost constant amount of about 4-5 ml O_2 during its adult life, although the rate of utilization is influenced by the ambient temperature (from Miquel et al., ref. 1).

EFFECTS OF MOST ENVIRONMENTAL FACTORS ON LIFE SPAN

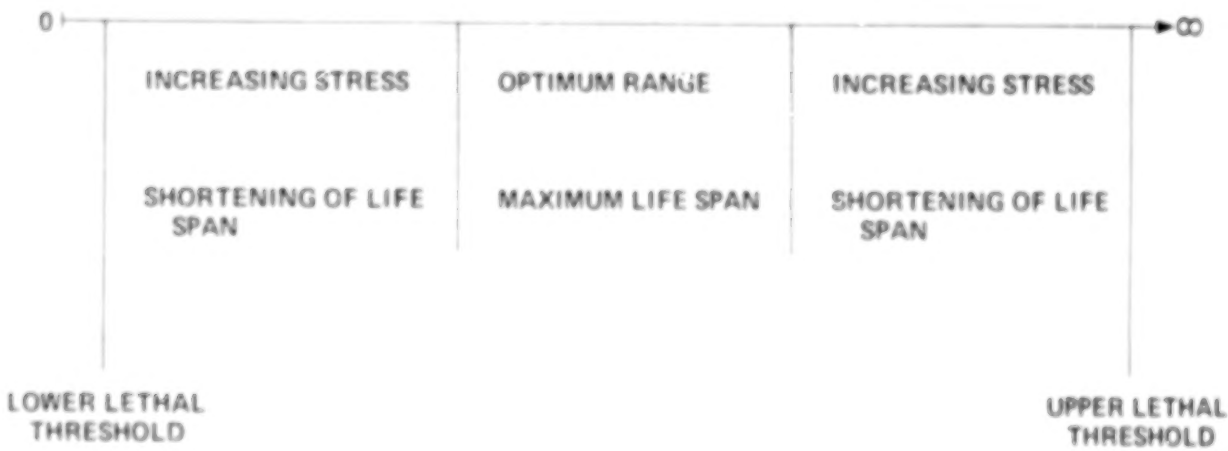

Figure 2.- Schematic representation of the relationship between the intensity of the environmental factors needed to sustain life and the lifespan.

TABLE 1.- SIMILARITY OF THE DETRIMENTAL EFFECTS OF NORMAL AGING AND OF EXPOSURE TO SPACE WEIGHTLESSNESS

Cardiovascular system				
Reduction in cardiac output	S		C	
Increase in blood pressure	S	A		
Respiratory system				
Decrease in vital capacity	S	A	C	
Musculo-skeletal system				
Decrease in grip strength	S		C	
Decrease in lean body weight	S	A	C	
Decrease in muscle mass	S	A		
Collagen increase in muscle	S			R
Fat infiltration of muscle	S			R
Bone demineralization	S	A	C	
Adrenal cortical function				
Decrease in urinary excretion of total 17-hydroxicorticosteroids	S	A	C	

S = Changes found in human senescence
A = Changes found in American astronauts
C = Changes found in USSR cosmonauts
R = Changes found in rats (exposed to weightlessness — 25 days in a KOSMOS flight)

animals, which (on the basis of the reported weight of about 300 g) were only about 2 m old.

Despite this accelerated aging of the musculo-skeletal system, if animals or human subjects were left to spend their entire lives in weightlessness, their lifespans might be significantly increased because of a reduction in metabolic rate. This agrees with calculations that suggest that about one-third of the calories ingested by man under normal conditions is used to provide energy to counteract the effects of gravity (ref. 6). Support for this concept has been obtained in both ground-based experiments and in observations performed during spaceflights. In fact, a recent article documents the reduced oxygen cost associated with treadmill walking in simulated subgravity environments (ref. 7). Also, "the energy cost of performing specific activities at one-g during training, wearing the Apollo space suit was higher than to perform the same activities on the moon surface at one-sixth-g." Moreover, both the speed and the efficiency of walking at reduced g were greater than could be achieved wearing a pressure suit in a 1-g environment (ref. 8). These observations are difficult to reconcile with the statement that "estimates of body composition from metabolic balance data, from preflight and postflight weights and volume, and from total body water and potassium provide no evidence for diminished caloric requirements during flight" (ref. 9). In our opinion, the high metabolic cost incurred during the Skylab missions may be linked with the specific dynamic action of the high-protein diet, which was at least twice the recommended dietary allowance, and with psychogenic factors associated with the heavy responsibilities of space travel. Also, we should keep in mind that astronauts and cosmonauts are usually engaged in exercise programs to maintain a high level of physical fitness

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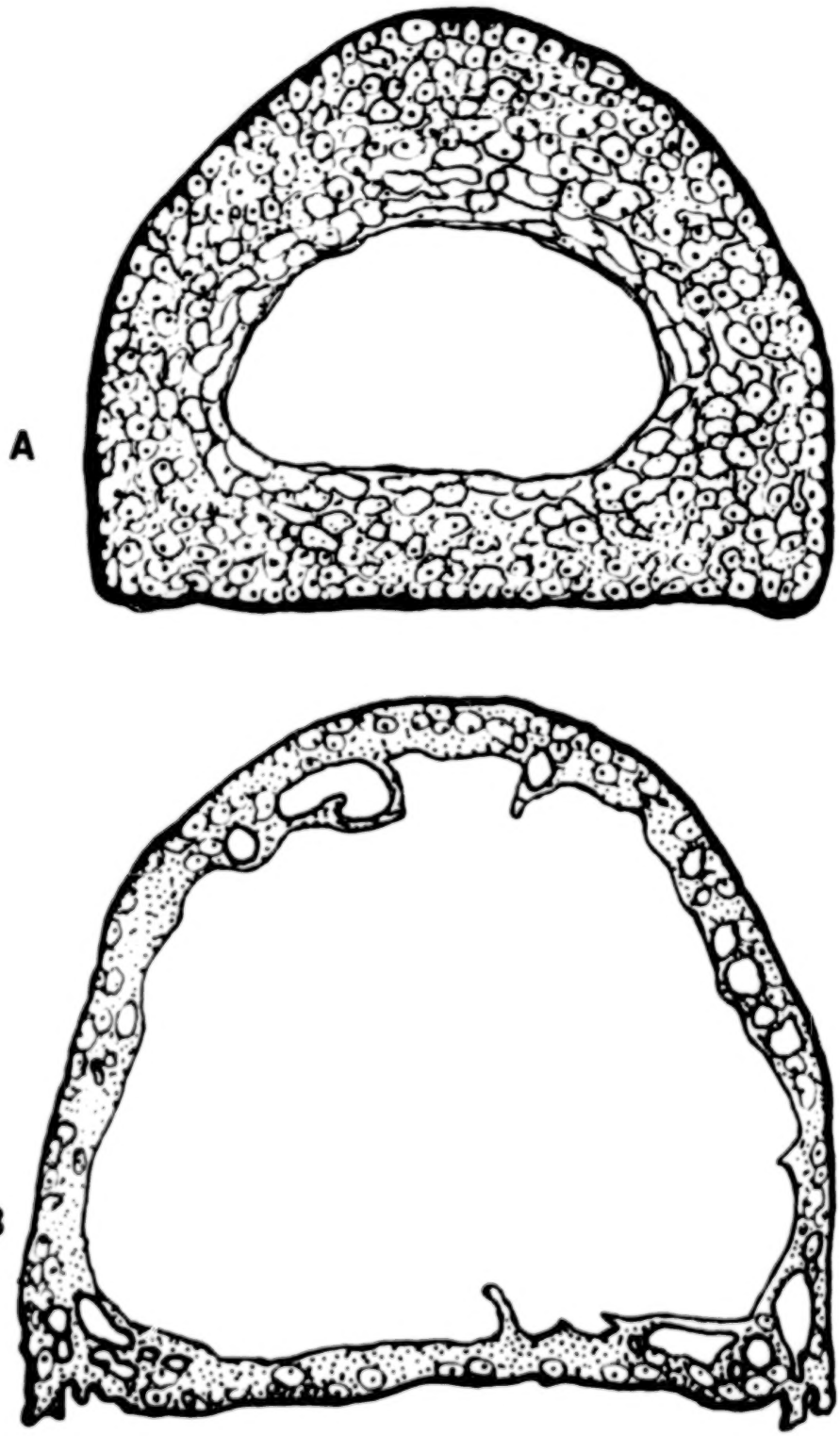

Figure 3.- Cross-section of the diaphysis of a phalanx. A) Normal bone of a 39-yr old female subject. B) Phalanx of a 90-yr old female subject. The bone is very thin and the medullary cavity much enlarged. (From R. Amprino and A. Bairati, Ztschr. f. Zellforsch. u. Mikr. Anat. 20:143, 1933.)

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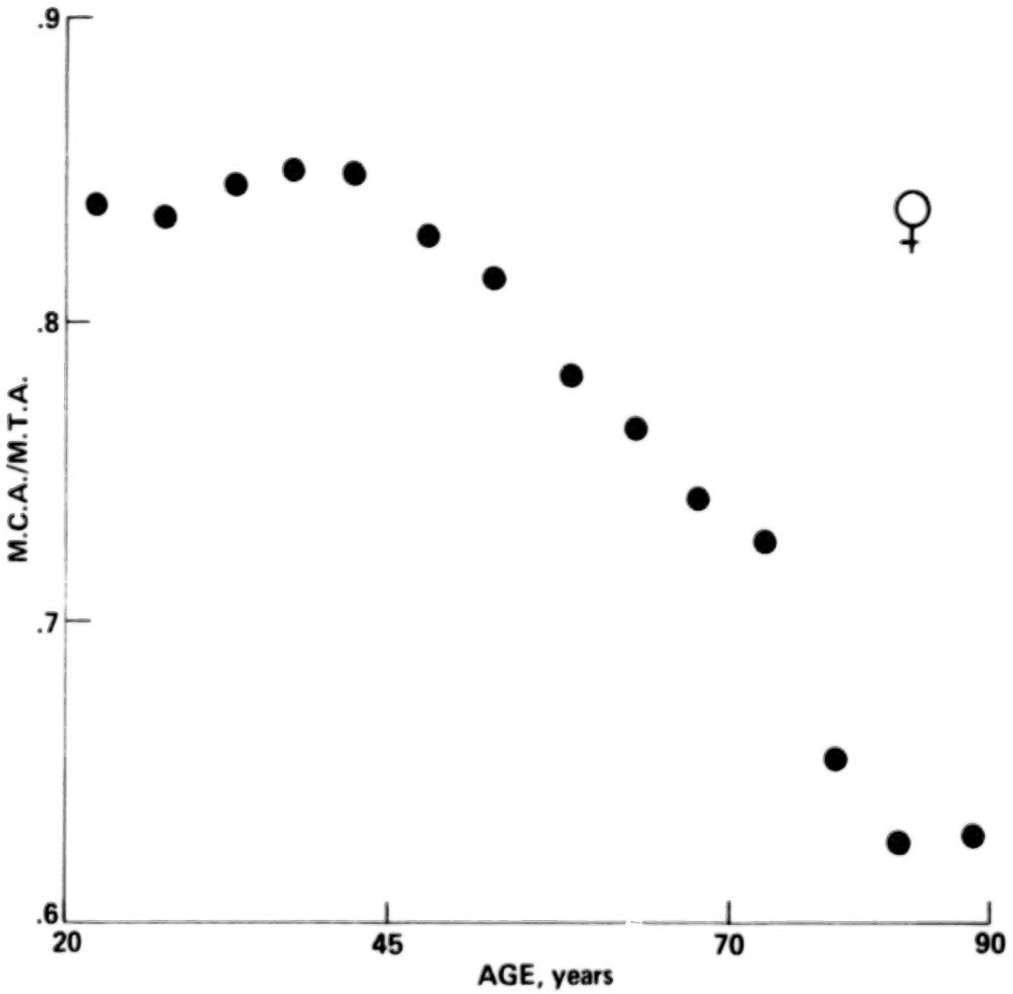

Figure 4.- Metacarpal cortical/total area ratios in normal premenopausal and postmenopausal women (means). From J. R. Bullamore et al., Lancet 2:535, 1970.

during space flight. Thus, the real effects of weightlessness are more likely to be clarified in experimental animals exposed to the space environment during long-duration flights. Preliminary observations by Soviet biologists have shown a gradual decline in motor activity of rats during the period of feeding in space on board a Kosmos biosatellite (ref. 10). This suggests that the feeding stimulus of rats decreases in the weightless state. Thus, if there is a decreased food intake at zero-g, long-duration spaceflights could increase the lifespan of experimental animals in a fashion similar to the feeding of hypocaloric diets (refs. 11, 12). The mechanisms involved would be essentially the same, namely a reduction in the level of metabolic reactions needed to sustain life and perform physiological work. This lowered metabolic rate would have a sparing effect on the time-dependent disorganization of cells and organs, which is manifested in physiological decline and, ultimately, death.

Perhaps the Shuttle program and even longer-duration spaceflights, in the future, will give us an opportunity to test the above hypotheses (table 2). We believe that gerontological experiments in space might contribute a new viewpoint to aid in understanding the biological effects of zero-g. Even more important, the study of aging in space might help to clarify the obscure relationships between environmental inputs and target organs, which modulate the rate of aging and set up a maximum lifespan for all higher organisms, including the members of the human species.

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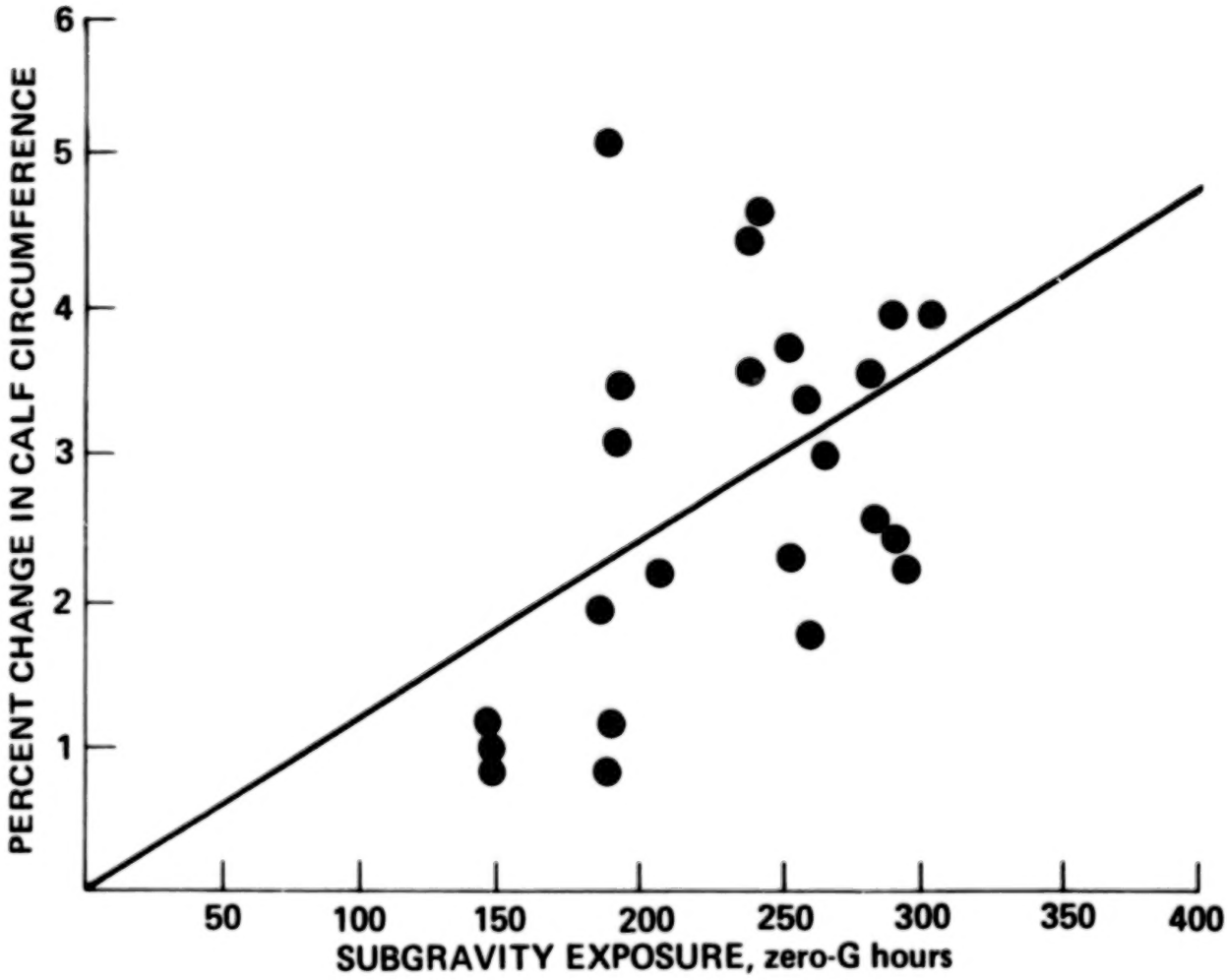

Figure 5.- Correlation between decrement in calf size and length of exposure to weightlessness (from G. W. Hoffler and R. L. Johnson: Apollo crew cardiovascular evaluations, in Biomedical Results of Apollo, NASA SP-368, 259, 1975).

TABLE 2.- PROBABLE EFFECTS OF VERY LONG-TERM EXPOSURE OF HUMAN SUBJECTS TO WEIGHTLESSNESS

1) Disuse atrophy of bone and skeletal muscle. After a certain period of exposure to zero-g, this condition could become irreversible to a certain degree and result in a syndrome similar to senile muscle atrophy and senile osteoporosis.
2) Decrease in the weight of most organs, with exclusion of brain.
3) Increased lifespan, associated with reduced food consumption? (G. H. Bourne calculated that in weightlessness the caloric requirements would be about 30% less than on the ground. However, the astronauts seem to eat normal or increased rations . . .)

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A PATHOLOGIST'S VIEW ON S OF VERY LONG EXPOSURE TO WEI NESS

Klaus Bensch

Stanford University School of Medicine

I am a little bit surprised at being here today, since I am not a gerontologist nor am I involved in monitoring the health of the astronauts. Basically I am concerned with pathology research, but only a few days ago Dr. Miquel informed me that he would like my comments on two subjects about which I can only speculate since no data are available. The questions are: 1) what are the probable consequences of exposure to weightlessness during periods of one year or more and 2) how would the effects compare with aging. In order to arrive at some tentative conclusions, I had to do some reading, mostly of the material published by NASA concerning the difficulties encountered by the astronauts. I have attempted to extrapolate from the material to try to predict what might happen if they stayed in space longer. My comments will be very uninformed and naive, but at the same time quite unbiased.

When an astronaut adapts to zero-g, he reaches a new state of homeostasis, and he is able to perform quite normally. An unexpected finding is the high food intake, despite expectations to the contrary. This may be somewhat related to the high levels of thyroxine that have been found in the blood of astronauts. Mental ability is not impaired, and apparently a new equilibrium is reached among the physiological subsystems reacting to the lack of gravity. However, potentially damaging reactions have occurred, including the loss of calcium and phosphorus from the bone and a certain degree of muscle atrophy. The increase in urinary excretion of hydroxylysine suggests that collagen is also broken down. Collagen in the extracellular space maintains the body structure and keeps the organs in place. If certain stresses are removed, collagen may be broken down, which is apparently the case in weightlessness. At this point we do not know if this process would continue in spaceflights of longer duration than those flown to date. Regarding calcium loss, it is likely that the loss will continue to the point of no return, causing serious incapacity upon returning to Earth. This would be the case if enough cells have become atrophic, impairing the ability of the organism to regenerate the musculoskeletal tissues lost.

I was amazed to find that fingernails do not grow as fast in space as on Earth. We cannot explain the reasons for this finding unless careful metabolic studies are performed to determine the efficiency of food absorption and utilization. The data suggest that somewhere, somehow, the calories are lost; perhaps there is a reduced absorption of nutrients during the intestinal passage. This could be a factor in decreased fingernail growth.

It is well known that in aged people the fingernails are thinner and grow at a slower rate. This is related to changes in the factors controlling the rate of mitosis in the epidermis. It seems that two of the substances influencing the rate of cell division in the basal layer of the epidermis are epinephrine and norepinephrine. Cell division occurs in a diurnal fashion; thus, when the cortisol level goes up and enough epinephrine is available the cells divide. Astronauts show some changes in their urine levels of metabolites of epinephrine and norepinephrine, and this may play a role in the decreased fingernail growth.

Returning to cell division and DNA synthesis, it is interesting to note that less uric acid seemingly is excreted in weightlessness. Since uric acid is an index of turnover of compounds important in DNA synthesis, this suggests a decreased cell division in some body tissue(s).

In discussing the major problems that may arise on coming back to Earth after a long exposure of one year or more to space weightlessness, a major complication is orthostatic intolerance. In weightlessness there is a shift of blood to the head and trunk. The astronauts experience fullness of the head and sinus congestion. Then, back at 1-g, on returning to Earth, the fluids shift in the opposite direction, that is, towards the legs, resulting in some circulatory problems. I wonder what might happen to the musculature of the blood vessels of the legs after a very long exposure to weightlessness. Will those muscle cells be able to reestablish a good tone around vessels normally subjected to gravitational stress? I am thinking of the blood vessels below the heart and especially those of the legs. It is probable that chronic exposure to zero-g may induce some degree of irreversible atrophy in the blood vessel musculature, which would result in a permanent impairment in circulation.

Another problem would be exercise intolerance, which has already been documented after flights in space. Obviously, the longer the duration of the flight the more serious this problem will be. The available data suggest that exposure to zero-g results in impaired ability of the cells to produce energy. This may last for weeks after splashdown and, following very prolonged space flights, could have an irreversible component.

Finally, I am going to mention neurological changes. These have been minimal, but they might be indicating some deterioration that could become serious in long-duration flights. The Achilles tendon reflexes were hyperactive upon reentry. This may be related to the muscle atrophy in the calf or to changes in the muscle spindles (which perceive the pull on the muscle). Whatever the mechanisms, there was an initial hyperactivity, then hypoactivity and, finally, the reflex became normal.

Now, what are the implications for the aging process? What will happen to older astronauts or scientists at zero-g if we superimpose the muscle and calcium loss induced by weightlessness onto their normal aging process? I believe this is a problem that should be investigated in future flight experiments.

I would also like to know the effect of weightlessness on tissue hypoxia. I am not talking about severe hypoxia but the moderate hypoxia that may occur on some tissue of aged subjects due to vascular changes. The circulatory change, triggered by zero-g may influence the oxygen tension of the tissues in a way that I cannot predict at this time.

The onset of edema during a spaceflight could be another problem. How would fluid elimination in cases of right heart failure be affected by weightlessness? Perhaps the lack of gravity would be beneficial, but the return to 1-g certainly could have catastrophic consequences.

If, as suggested by some studies, weightlessness exerts an influence on collagen metabolism, this could be of some consequence in the process of scar formation in subjects exposed to surgical interventions in space. Even if wounds heal well in space, they could reopen on return to Earth if the tensile strength of collagen synthesized in space is deficient.

Now, focusing on cell biology, we may ask ourselves what we can do to investigate some fundamental responses to weightlessness. We can try to correlate physiological reactions with changes at the cell and organ level. This would give us some insight about the rate of aging in space. In my opinion, this problem is related to the concept of consumptive anoxia, which happens, for instance, in some nerve cells of epileptics. These cells live at so high a rate that they get exhausted and experience atrophy. This is associated with increased O_2 consumption and, on the basis of unevenness of blood flow, some cells may be more affected than others. The contrary situation may also occur, which is relevant to the problem of disuse atrophy of the leg muscle. The basic question is: Can interneurons die when they are not used? Apparently, this can be answered in the positive, the best known example being what happens in blindness. In this condition the interneurons, which are a link in the chain between the retina and the brain center, become atrophic and actually die, which can be seen in individuals who are blind in one eye. The neurons of certain layers of the lateral geniculate body vanish. We can speculate that a similar process will occur in certain areas of the autonomic nervous system of individuals living in space for a long time. Here the time of exposure of the concerned neurons to the decreased functional demands is of the essence, because the regenerative potential of the nervous system has been documented many times. This area of the reversibility or nonreversibility of neuromuscular atrophy in experimental animals and human subjects exposed to weightlessness needs to be clarified by spaceflight experiments.

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HUMAN HOMEOSTASIS IN THE SPACE ENVIRONMENT:

A SYSTEMS SYNTHESIS APPROACH

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INTRODUCTORY REMARKS

It is an honor to have the opportunity to address a group of distinguished gerontologists, biologists, and space biologists.

That I am here today talking about space biology and space gerontology is the result of a random encounter with Jaime Miquel; it has proved to be a random encounter of the best kind.

I am grateful to the NASA Life Sciences chiefs, Drs. M. Sadoff, D. Feller, H. Sandler, J. Sharp, and H. Klein, whose support has made my continuing collaboration with Jaime possible. In addition, I want to express my appreciation to Dr. Comfort, whose consideration and encouragement during my first groping steps into the field of gerontology have provided a strong positive reinforcing stimulus and an occasional reassuring pat on the shoulder.

What I wish to accomplish in this presentation is to clarify some notions related to a working knowledge of human homeostasis and the kind of "shifts" or "resettings" the various homeostatic control systems suffer in the space environment. Near the end of my presentation, I shall attempt to put the main conclusions from a preliminary systems synthesis in a nutshell — a rather soft shell some may find, reflecting the limitations in available biomedical data from past spaceflights. A considerable handicap for such a synthesis is that, apparently, no large-scale systems analysis served as a guideline for the experiments that were performed. Rather a kind of piecemeal approach has been used, some experimenters studying only a "cardiovascular man," so to speak, others only a "neuroendocrine man," and so forth. (The situation is actually worse: the "cardiovascular man" was further "dissected"). This is not too detrimental for gathering data but might generate the danger of disobeying one of the ten commandments of systems physiology, namely: "Thou shalt not commit oversimplification."

Along the way, I will touch upon various background themes related to space biology and medicine. I will discuss some testable hypotheses concerning possible effects on homeostasis that long-term exposure to weightlessness might cause, a theme of genuine space-gerontological character. Finally, I will propose an hypothesis concerning a problem in the field of metabolism, a solution to which could be facilitated by an experiment in space.

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HISTORICAL PERSPECTIVE

Future directions in space exploration have not crystallized as yet in the present period of consolidation of past achievements, reconsideration of goals, and reformulation of objectives to meet future challenges. With two eventful decades of space missions just behind us, a synopsis and evaluation of the major achievements are in order.

Among the technological milestones in this first chapter of space history, we can single out the first orbiting satellite, the first man in orbit, and the first man on the Moon; these were clearly the most important and logical steps in the path opened for the conquest of space. (Recent planetary explorations open another exciting chapter of space history.) Of equal importance were the following major events in the short history of space biology and medicine:

a) Demonstration that a terrestrial mammal (dog) could withstand the accelerations of spaceflight and short-duration exposure to weightlessness.

b) Demonstration that man is capable of adapting to weightlessness for a period of at least 3 months, without any irreversible impairment of his capacity to readapt to the terrestrial environment.

In the decade that preceded the first spaceflights (i.e., around 1950), many dire predictions had appeared in the literature about the effects that weightlessness may have on living beings in general and human beings in particular. This must have been a fascinating era, which I missed, unfortunately, because I had just graduated from kindergarden. Today we may read about those predictions with a smile, but 20 years from now our hypotheses and concerns regarding long-term exposure to weightlessness may be equally amusing. This thought has considerably tempered both my optimistic and pessimistic hypotheses. Prophecy is a risky business in general, but even more so in science.

The following instructive example illustrates this point. Only a few years before the manned Skylab missions, concerns were expressed regarding the quality and quantity of sleep in space. These concerns were based on sound scientific reasoning. ". . . If the weightless state reduces tonic sensory influences from deep somatic structures, and from graviception in vestibular and vascular systems, it might be anticipated that modification in sleep patterns would occur in ways resembling the effects of spinal transection . . ." (i.e., reduction of sleep duration to 5 hours and increase of the light-sleep phase, W. R. Adey, 1971). However, this is not how one of the Skylab astronauts felt: ". . . The scientist pilot commented on how pleasant it was to sleep in space, and he felt that he was receiving approximately the same amount of sleep as he was accustomed to on the ground . . ." (Skylab III report). He even said he did not mind getting up in the morning because he knew he could go to sleep again in the evening!

This, nevertheless, does not mean that the predictions were completely wrong. It just happened that a simple countermeasure was available in this case, a restraining "sleeping bag," which prevented floating-around movements and bouncing of the sleeping astronauts against the walls of the cabin; it also gave them more of the feeling of sleeping on Earth. Unfortunately, it appears at this time that developing countermeasures for other effects of weightlessness will not be as simple.

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SOME NOTIONS FROM GRAVITATIONAL PHYSICS

Especially for the benefit of our gerontologist guests, I shall discuss now the three possible situations in which an object can find itself with respect to the Earth's gravitational field. First it can fall. Note (fig. 1) that in this condition of free-fall the object is in a 1-g field. However, for a sufficiently small

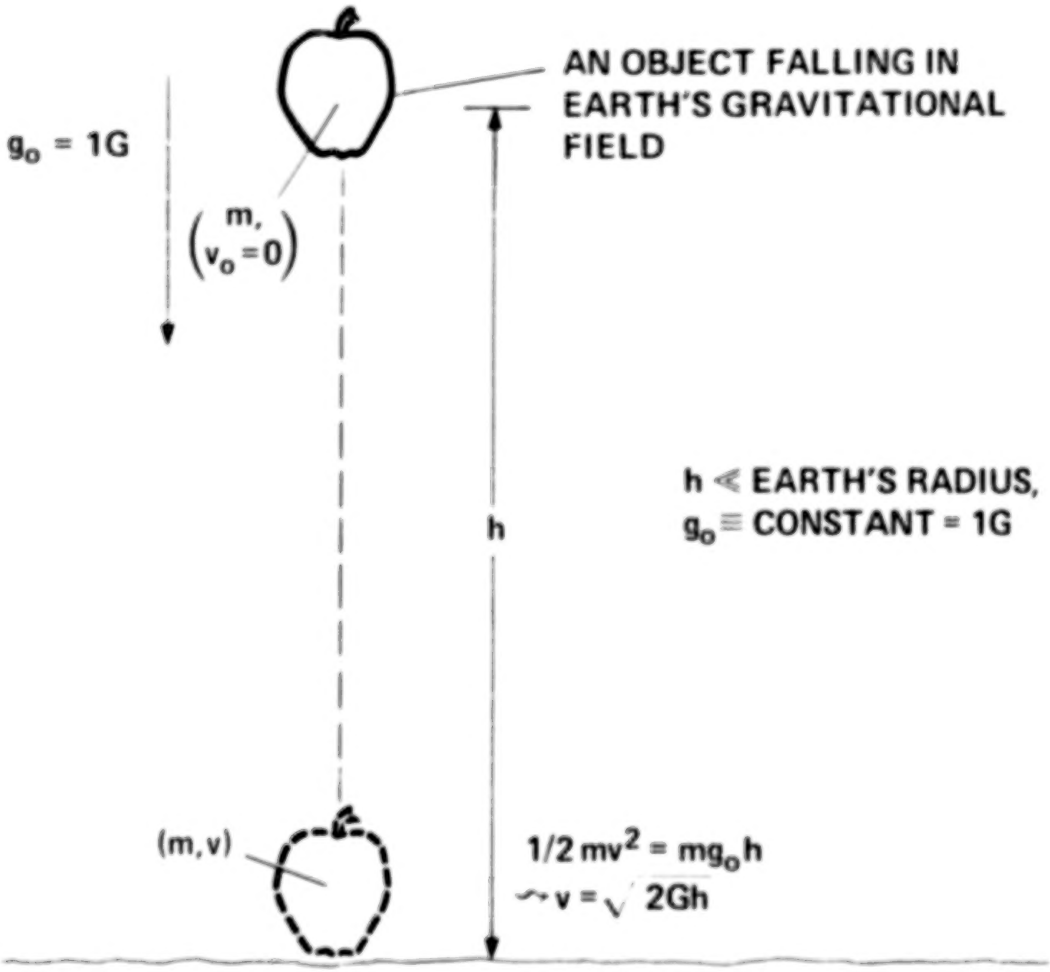

Figure 1.- The mechanics of fall of an object (say an apple) in a 1-g gravitational field.

object and a long free-fall path, as in the case of a rain droplet falling on Earth, the resistance of air increases as the object's speed increases on falling, to finally become equal with the gravitational force. Thereafter, the object's speed remains constant and the object is no longer in an acceleration field. A special case is free-fall in water. During resulting total immersion, Archimedian buoyancy comes into action and again the object is in a weightless state (e.g., scuba divers. Did you know that a scuba diver swimming under the frozen surface of a lake can actually walk upside-down on the inner surface of the frozen water layer?).

Second, the object may orbit the Earth (fig. 2). In this case, although it is still in Earth's gravitational field, a condition of weightlessness is established for an observer located on the object due to the centrifugal force.

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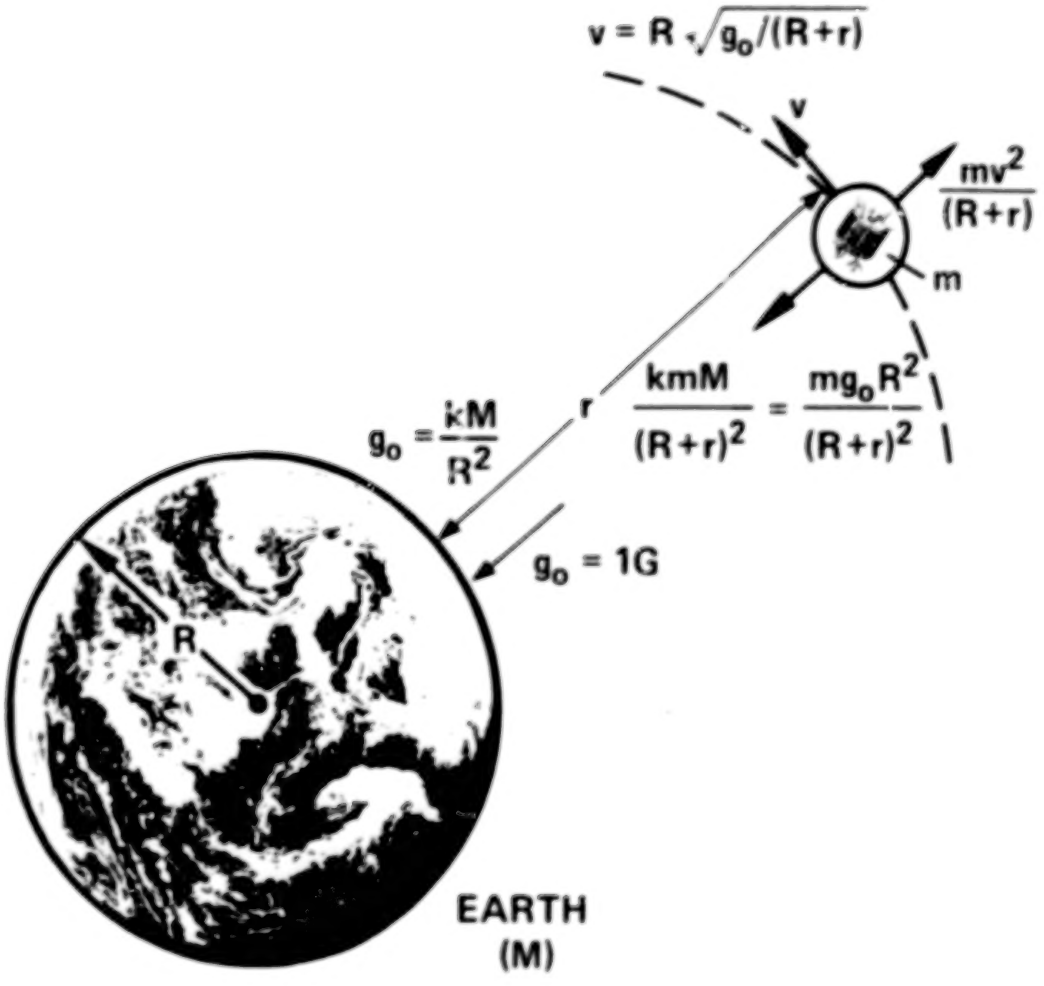

Figure 2.- The mechanics of satellite motion.

Finally, the object may be able to escape terrestrial gravity (fig. 3). In that case, it reaches a condition of virtual weightlessness when it is far enough from Earth and any other large object (planet, star, etc.). Unfortunately, actual weightlessness cannot be achieved on Earth, except for very short periods (for instance, for 60 sec during parabolic flights of aircraft). Many of the physiological effects of weightlessness, however, can be simulated in various ways on Earth, as we shall see later.

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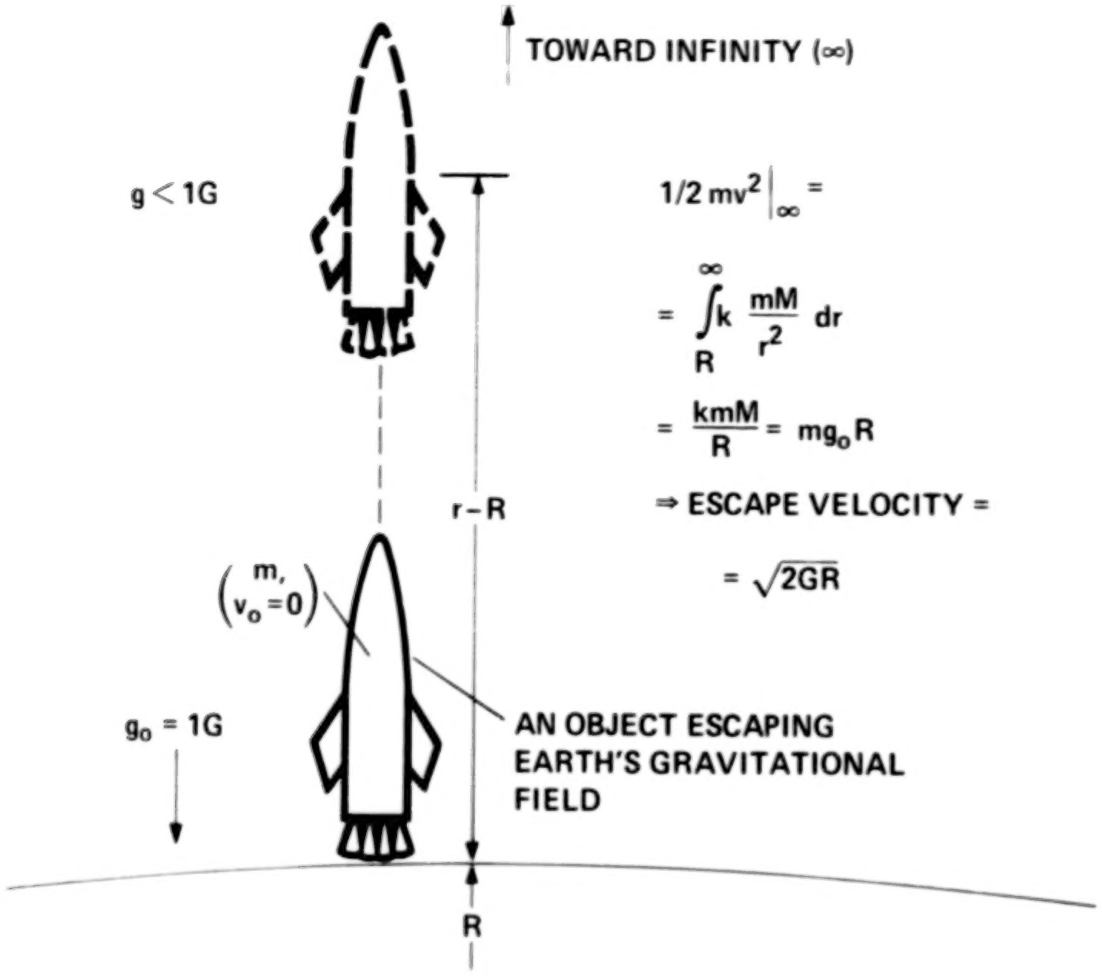

Figure 3.- The Newtonian mechanics of escape of an object (say a rocket) from terrestrial gravity.

WEIGHTLESSNESS VERSUS HYPERGRAVITY

An interesting question is whether the physiological phenomena associated with the transition from one- to zero-g are mirror images of the effects of "hypergravity," which is achieved by centrifugation. Unfortunately, centrifugation studies have been mainly directed toward investigating the effects of more or less large accelerations, apparently with spaceflight accelerations during takeoff and reentry in mind. It has actually been hypothesized that there is such a symmetry. In my opinion, there is insufficient evidence to support such a view, and in some cases it can be seen even on theoretical grounds that this may not be the case; this depends largely on the mechanism by which gravity affects a physiological function at hand.

For instance, seeing from figure 4 that hypergravity retards growth, would you expect that zero-g will accelerate growth and lead to production of larger animals? This is an intriguing question that may be of both theoretical and practical importance. The question of symmetry between the effects of hypergravity and weightlessness can be studied only by planning specific experiments to be performed at zero-g and at 2-g (as well as at one or two levels on both sides of 1-g). Higher g fields studied in the past probably cause homeostatic changes beyond the dynamic ranges the

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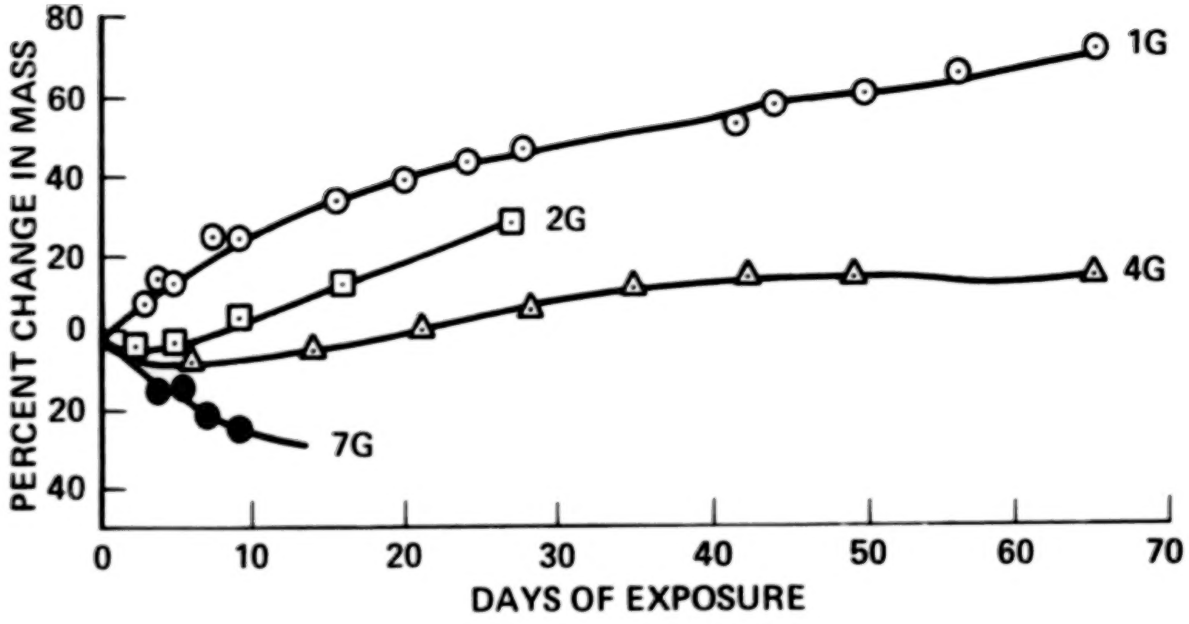

Figure 4.- Growth pattern of developing white mice (5 weeks old) during exposure to altered G. (Redrawn from Wunder and Lutherer, 1964)

organism has evolved to cope with, thus causing "stress" and nonlinear responses that obscure the question of symmetry.

An interesting experiment in hypergravity was done by A. H. Smith and coworkers on chickens. (Why does one study chickens if one is interested in the responses of humans? Well, I am not sure. Could it be the fact that they are, as we are, bipeds?) Centrifugation at 5-g resulted in a rather high mortality rate of chickens; however, if those animals that survived were mated, and this was repeated with the survivors of the second generation and so forth until the fifth generation, then survival was increased by 15%. Clearly, artificial selection favored animals with the physiological characteristics that made them resistant to centrifugation.

BED REST AS A SIMULATOR OF WEIGHTLESSNESS

Centrifugation is the method of choice for simulating hypergravity. On the other hand, it has been held for some time that horizontal bed rest is the best method for simulating the physiological effects of weightlessness on Earth. However, a simple evolutionary reasoning would indicate that an even better simulation of weightlessness can be achieved by using a slight head-down tilt (see fig. 5).

In fact, our early ancestors used to move around in the quadruped position until the upright posture was ventured, despite the various physiological disadvantages associated with it (including the risk of getting flat feet!). This posture had survival value (selective advantage) for our primitive ancestors that overshadowed the disadvantages, and it has remained with us ever since. (Or maybe this is because we liked it — let us not forget that as babies we are quadrupeds, and an externally forced programming is responsible for our acquiring the biped posture.) However, our bodies still contain homeostatic systems adapted to the horizontal posture. As

"HEAD DOWN (-4°) BEDREST BRINGS ABOUT MORE RAPID DEVELOPMENT OF CHANGES IN HAEMODYNAMICS, FLUID DISPLACEMENT AND NERVOUS TONE THAN TRADITIONAL RECUMBENT (0°) BEDREST"

Figure 5.- Antiorthostatic bed rest. (Quotation from Krupina et al., 1976.)

a matter of fact, most of us spend about a third of our lives in that position (sleep). Therefore, it can be expected that horizontal bed rest will simulate the effects of hypodynamia associated with the lack of gravitational load in weightlessness. It may also simulate, to some extent, fluid shifts and related phenomena due to disappearance of hydrostatic pressure normally present in the blood circulation on Earth. Nevertheless, the simulation will have limitations due to the fact that a) we are to some extent adapted to the horizontal posture and b) when lying in bed and during bed rest studies, the head is always a few degrees higher than the rest of the body, because of the pillow and mattress. Therefore, a rush of blood to the head, which occurs in weightlessness, will be minimal in bed rest. (The invention of the pillow may have been inspired from our physiological need to prevent such a shift of blood to the head during sleep.)

It is instructive to compare classical horizontal bed rest and headdown bed rest. Apparently, there is paucity of American investigations with "antiorthostatic bed rest" as Russians call headdown bed rest; the Russians, on the other hand, have performed a number of studies since 1970 and have documented its superiority as a simulator of weightlessness. Figure 6 depicts Russian data on the effect of the orthostatic test on heart rate at horizontal bed rest and bed rest with various headdown tilt angles as well as in weightlessness.

BIOLOGICAL EFFECTS OF WEIGHTLESSNESS

Very small organisms having no circulatory system and no skeletal system will probably have only orientation problems while in weightlessness. An interesting case is that of the spider, Arabella. On Earth she was making well-structured, aesthetic webs, but not in her first days in Skylab. She was, however, able to adapt later and perform reasonably well.

Human beings, having bipedic posture and a resulting hydrostatic pressure in blood circulation, have more than just disorientation problems in weightlessness at the beginning of their exposure. On Earth, the compliances of the vascular beds of the legs and head have adapted in the course of our evolutionary history to accommodate high and low blood pressures, respectively, because of hydrostatic pressure. When hydrostatic pressure disappears in weightlessness, there is too much compliance in the legs and too little in the head. There is, therefore, an immediate tendency of the blood to shift toward the head, which is experienced as a rush of blood and subsequent continuous head fullness and nasal congestion. The head fullness is of

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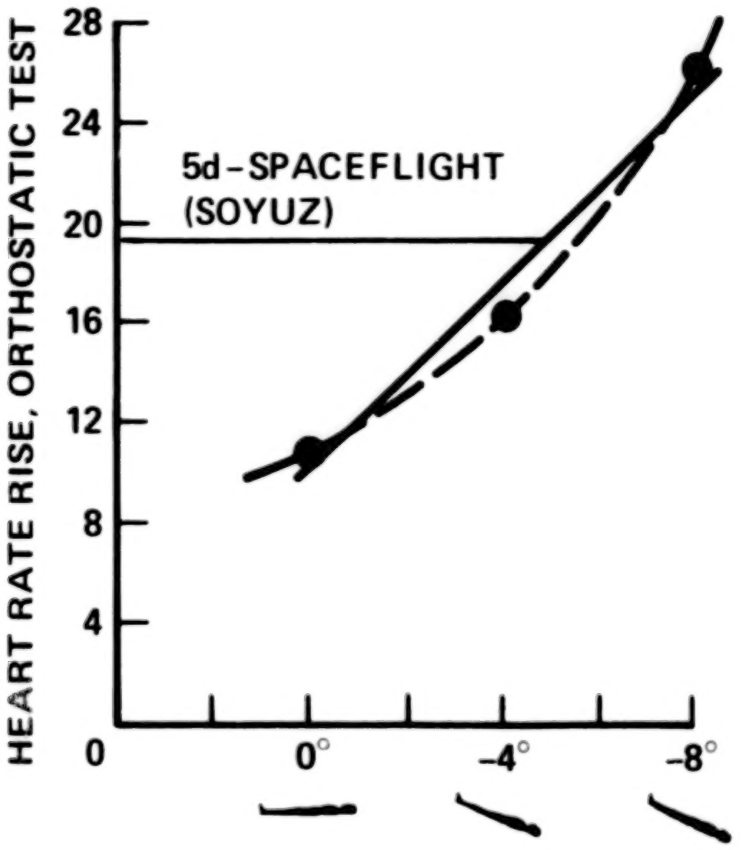

Figure 6.- Effect of type of 5d-bed rest on heart rate rise. (Data from Kakurin et al., 1976; experiments performed after spaceflight or bed rest.)

such magnitude that it can be clearly seen when comparing with the form of the face on Earth.

CHANGES OF HUMAN HOMEOSTASIS IN WEIGHTLESSNESS

Table 1 summarizes the salient features of homeostatic changes during adaptation to the weightless state. This is my preliminary evaluation based on published Skylab data. In more detail, these changes are as follows.

Heart rate. Under the conditions of both resting and of submaximal exercise or lower body negative pressure, heart rate was generally elevated by roughly 20% in flight and on the first day of recovery when compared with preflight values. Resting heart rate showed a slight tendency to decrease toward preflight values with a longer period in weightlessness. It was not elevated in Skylab 2. No explanation of this phenomenon has been offered in the published reports apart from noting that a decrease rather than an increase of heart rate had been expected.

Plasma volume. On the first recovery day, plasma volume was 15% less than before flight.

Red blood cell mass. An unexpected finding (as stated in a published survey of the Skylab data) was a 15% decrease of red blood cell mass on recovery when compared to the preflight value.

TABLE I.- METABOLIC-CARDIOVASCULAR CHANGES IN WEIGHTLESSNESS

A TENTATIVE EXPLANATION

RED CELL MASS (RCM):	↘ 15%	THEORETICAL PREDICTION:
PLASMA VOLUME (PV):	↘ 15%	TOTAL METABOLIC RATE
HEART RATE (HR):	↗ 20%	(MR): ↘ 30% (DUE TO
CARDIAC OUTPUT (CO):	↘ 30%	WEIGHTLESSNESS)
STROKE VOLUME (SV):	↘ 40% →	COMPUTED FROM: CO = HR·SV
BODY WEIGHT (BW):	↘ 5	

PRINCIPLE OF EXPLANATION

1 MR ↘ 30% → CO ↘ 30%;

2 BLOOD VOLUME ↘ 15% (: GAUER-HENRY EFFECT) → PV ↘ 15% AND RCM ↘ 15% (: INHIBITION OF FORMATION);

3 HR ↗ 20% (?STRESS?) AND SINCE CO ↘ 30% → SV ↘ 40%

4 BODY WEIGHT LOSS WILL BE THE RESULTANT OF BLOOD VOLUME LOSS (1%), EXTRACELLULAR FLUID LOSS (?), CALCIUM AND NITROGEN LOSS. (IN SKYLAB 4 LESS BW LOSS BY HIGHER CALORIC INTAKE: INCREASED BODY FAT?)

Cardiac output. Cardiac output during submaximal exercise on the first recovery day was decreased by 30% when compared to preflight value.

Negative fluid balance. This was observed during the first week in flight but its exact magnitude has not been reported, except as being of the order of 1 liter.

Body weight. At the middle of the flight, body weight was decreased by 1-3 kg in the various crewmembers (and somewhat more on recovery, the last additional decrease being clearly due to the increased activity in the week before reentry); the reported hypothesis favored caloric deficiency (metabolic cost of spaceflight higher than theoretical).

Bone calcium. The loss was at the rate of 0.4% of total stores per month (equivalent to 4 g/month).

Muscle. This was lost (negative nitrogen balance) at the rate of 4 g/day.

Readaptation. Upon return to Earth, cardiovascular indices returned to preflight levels in 21 days for Skylab 2 (28 day mission), 7 days for Skylab 3 (56 day mission), and 5 days for Skylab 4 (84 day mission). The daily levels of exercise in flight were, respectively, 1/2, 1, and 1-1/2 hr; this by itself could explain the shorter readaptation time with longer duration of mission. However, the highly nonlinear relationship between duration of exercise and readaptation lag (see fig. 7) is not readily explainable. An alternative interpretation of the data could be that a remarkable deconditioning specifically followed the Skylab 2 mission (for some

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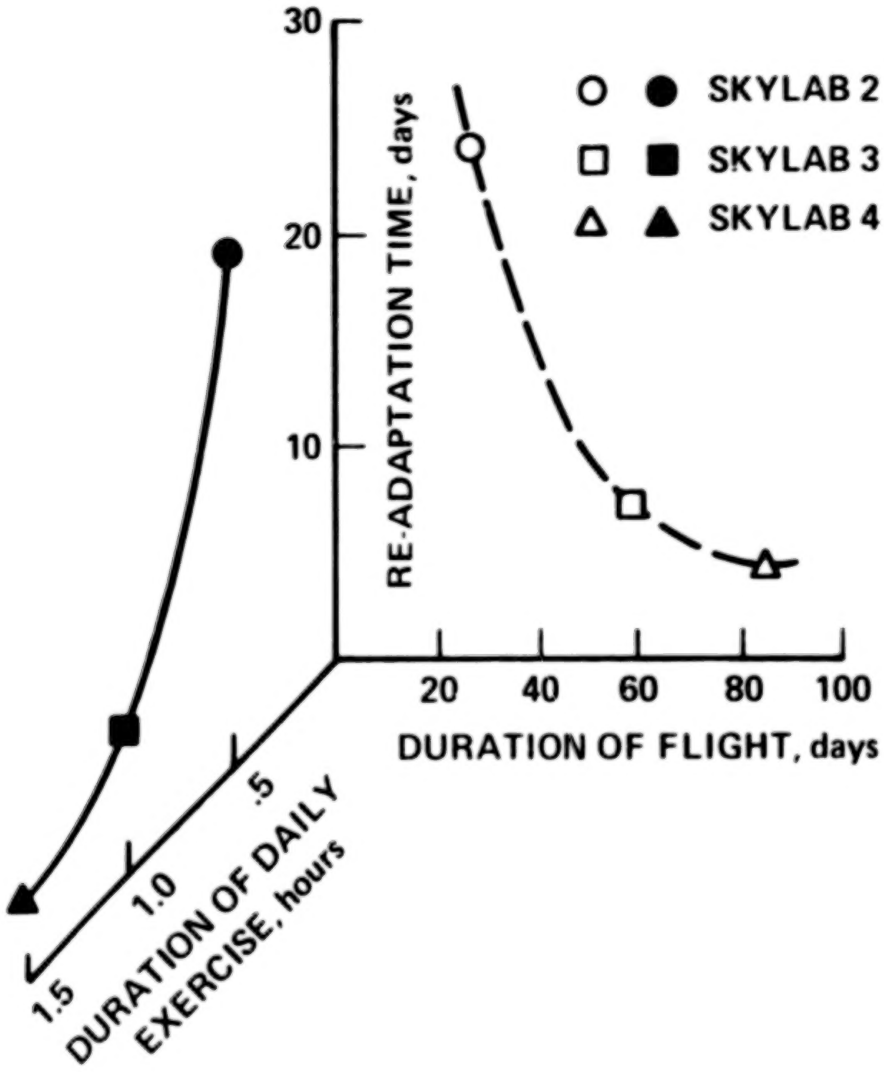

Figure 7.- Observed relationship between duration of flight, duration of daily exercise in flight, and readaptation time after return to Earth.

unknown reason), whereas after Skylab 3 and 4 cardiovascular readaptation took approximately the same time (about a week) irrespective of the amount of exercise. This interpretation gains some plausibility when one observes that cardiovascular adaptation to weightlessness (i.e., establishment of new steady states) also requires approximately one week for its full development.

ADAPTATION TO WEIGHTLESSNESS

The fact that the human organism is able to adapt at all to the condition of weightlessness is considered admirable, especially since this is an adaptation to an environment in which terrestrial animals have not evolved. In accordance with the concept of homeostasis of the internal milieu of the organism (Claude Bernard, Walter Cannon, and others), that is, the capacity to preserve a constant internal environment in the face of environmental changes, it had been assumed that man might not be capable of adapting to an "exotic" environmental condition such as weightlessness, a condition never encountered by our ancestors in evolutionary history. This notion

is based on the misconception that an animal, placed in a new environment, adapts to that environment per se. Rather, I believe that an animal adapts, not to an environmental condition, but to the effects of that condition on the internal environment of the organism. I think that only this view can lead to a meaningful systems analysis and synthesis of the effects of weightlessness on the human body.

Specifically, this approach consists of identifying changes that may result in the internal milieu during long-term exposure to weightlessness and the mechanisms that have evolved to adapt to those changes (when they had been encountered in evolution separately and on various occasions as a result of various environmental inputs). Such a synthesis should be directed toward delineating metabolic and other physiological costs of spaceflight compared to living on Earth, identifying possible irreversible changes, and evaluating the possibility of an altered aging rate in weightlessness; long-term and evolutionary consequences for permanent human colonies in the weightless state should also be outlined. Further, the effect of the state of the physiological systems of a given astronaut on his adaptation capacity should be assessed, for which a specific methodology not yet available in gerontology will have to be developed, chiefly for determination of biological age. Finally, the problem of assessing changes during short-term exposure to the space environment will have to be addressed.

HOMEOSTASIS IN SPACE CLOTHING: FRAGMENTS OF A SYSTEM SYNTHESIS

As I said earlier, separate groups of investigators have studied each aspect of homeostatic shifts in weightlessness and have reported the above findings more or less separately. From the systems physiological point of view (I could even say, from the body's point of view!), the physiological significance and the mechanisms of such changes can be evaluated and elucidated only when a systematic effort is made to integrate all the findings. Such an integration is made somewhat difficult when one has at his disposal only the published reports on the various studies, in which the data may already have undergone some "filtering out." In addition, as I mentioned earlier, gaps or blind spots are bound to creep into the matrix of the findings due to the absence of a systems planning of the studies. Despite these difficulties, I have risked a preliminary systems synthesis of the published data and have attempted to uncover the mechanism underlying the observed homeostatic responses to weightlessness.

Decrease of Cardiac Output

It had been calculated, as long as two decades ago, that one-third of the daily calories expended by human subjects are utilized in counteracting the pull of gravity; a 30% decrease of basal metabolic rate in weightlessness was therefore expected. On the other hand, it has been established during the last ten years that increased or decreased metabolic demands by the body tissues influence cardiac output proportionally, that is,

$$\text{cardiac output} = K.\ BMR$$

where BMR stands for basal metabolic rate. Thus, a 30% decrease of BMR in weightlessness would result in a 30% decrease of cardiac output under both resting and exercise conditions, as was found.

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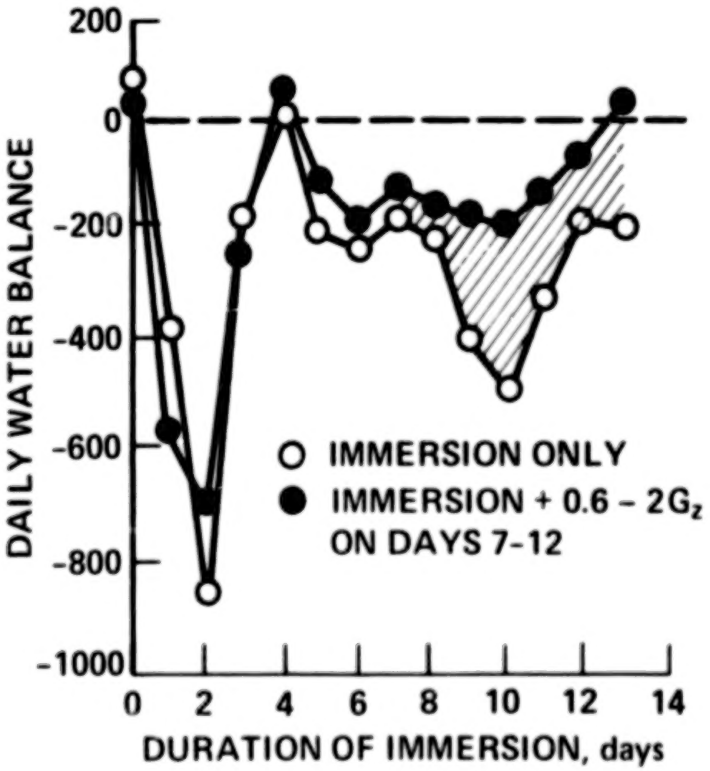
Negative Fluid Balance

This had been predicted by Gauer and Henry in the 1960s. My guess is that the disappearance of hydrostatic pressure in weightlessness and the difference in vascular compliance between head and legs cause the blood to shift from the legs towards the thorax and the head, as I have already mentioned. Fluid accumulation at the thorax level initiates a response of the fluid volume control system (which in some way monitors blood volume at the thorax level)[1] resulting in forcing the excess fluid out of the body. A new steady-state condition of fluid balance is then established within about 5 to 7 days. This finding correlates with observations in simulated weightlessness, such as body immersion in water (see fig. 8). The small continuous negative fluid balance after day 6 may be due to the fact that immersion in these studies was not complete, the head being kept above the water surface.



TOTAL WATER LOSS, ml		
DAYS	GROUP I (○)	GROUP II (●)
0-6	1887	1650
7-13	1956	647

Figure 8.- Negative water balance during immersion.
(Data from Shuzhenko et al., Moscow 1976.)

[1]When the venous return of the heart is either decreased or increased, the change is "sensed" by baroreceptors (acting as stretch receptors) located in the left atrium of the heart (Schmidt-Nielsen, personal communication).

Plasma Volume Decrease

It is reasonable to assume that the observed 15% decrease in plasma volume will correspond to a 15% decrease in blood volume, which is due to the blood shift discussed above. We can arrive at a rough estimate of the obligatory blood loss as follows. If the blood were distributed along the body roughly in proportion to each part's length (a reasonable assumption for the sake of the present argument), then it can be seen that on Earth about 1/5 of the blood volume is above heart level and 4/5 are below it. Since hydrostatic pressure in the part of the circulation below the heart is a linear function of heigh. (distance of each point from the ground), the amount of blood from each point that shifts toward the thorax on entering the weightless state will be proportional to its distance from the heart. If we assumed that this shift is 100% from the sole of the feet and 0% at the heart level, then one-half of the blood below the heart, that is, 2/5 of the total amount of blood, would shift upwards. Using similar reasoning, it is clear that of this upward shifting blood volume, only one-half or 1/5 of the total will be accommodated in the upper part of the body; the other 1/5 or 20% will have to be lost from the body. This figure is close to the observed value of 15%. The small difference could be due to the obviously unrealistic assumption that all the blood of the soles shifts upward.

Quite possibly, the amount of fluid actually lost from the body will be, in absolute magnitude, about twice as much, because there is an equilibrium between blood and extravascular fluid. Thus, given the fact that the volume of blood of a 70-kg man is about 5 liters (7% of body weight), the plasma volume will be roughly 2.5 liters, so that plasma loss will be about 0.4 liter, or a total blood loss of 0.75 liter. Therefore, extravascular fluid loss will be 0.75 liter, and the total fluid loss will be approximately equal to 1.15 liters. This is in good agreement with the reported value of approximately 1 liter.

Decrease of Red Blood Cell Mass[2]

Loss of red blood cell mass (15%) had been observed even in Apollo missions; at that time it was attributed to the pure oxygen atmosphere used in those missions. Thus the published summary report of the Skylab data stated that it was not expected that the same loss would occur in the Skylab missions. Moreover, it was hypothesized there might be a tendency for a further decrease during longer spaceflights which, however, would be counteracted by a kind of "governor system" that would not allow a loss of red cell mass greater than 15%. It was proposed that such a "governor" mechanism should be sought in the human organism also on Earth. However, from a systems physiological point of view (or from any point of view for that matter!), it is not clear how such a figure of "15%" could be a general characteristic of the organism, or why it should be a critical level. However, there is a simple alternative explanation which directly follows from the discussion on plasma volume decrease. That is, since plasma volume decreased by 15% in spaceflight, red blood cell mass would have to decrease also by 15% to counteract changes in the

[2]This subject is more extensively discussed elsewhere (A. C. Economos (1981): Regulation of haemopoiesis in altered gravity. Biol. Revs. 56: 87-98).

hematocrit.[3] This view is strengthened by the fact that no evidence for a higher red blood cell destruction rate in space at steady state was found and the decrease is thus due to reduced production.

Bone and Muscle Loss

Muscle loss in weightlessness is probably due to both reduced blood flow to the legs and hypodynamia (disuse atrophy). Bone loss, on the other hand, may be attributed to lack of stimulation of the skeletal system (mainly weight-bearing bones), due to both weightlessness and hypodynamia. In an evolutionary framework this should be expected, since bone was an "invention" of the terrestrial animals to counteract gravity; thus the bone mass is set by the body weight, not mass, that is, by gravity. The first to recognize this was Galileo, who theorized that an increase in the size of the animal (increase of bone length) should be paralleled by more than proportional increase in bone cross section to bear the extra load without breaking (see fig. 9). A similar relation would hold for a change from 1-g to higher g (fig. 10). What will happen in very long exposure to weightlessness is a question mark at this moment! (See fig. 11.)

It may be instructive to contemplate the case of sea mammals, which supposedly came (back) to the sea from the land many millions of years ago. (This is an interesting evolutionary "experiment" which can provide valuable insights.) The weightlessness caused by buoyancy (Archimedes' principle) has led to evolution of different ratios of bone/body mass in sea mammals when compared with terrestrial mammals of the same body mass. Thus, a porpoise's and a whale's bone masses are similar proportions of their body weight, while in terrestrial animals bone mass increases faster than body mass (roughly as $(\text{Body Mass})^{1.15}$, as has been empirically established). This is because of a principle which, as I said, was recognized first by Galileo in 1638, namely, that gravitational load increases proportionally to L^3, while strength of bone increases only as its cross section or L^2, where L represents a linear dimension of the animal's body. Therefore, if bone increased proportionally with the rest of the body, it would lag in strength and collapse. According to this reasoning, however, bone mass should have to increase not as $L^2 \times L$ but as $\text{Load} \times L$ or as $L^3 \times L$, that is, L^4, which is proportional to $BW^{4/3}$. This is a little over the empirical value $BW^{1.15}$. Thus, the "limbs" of the sea mammals atrophied as they adapted, and bone was lost because gravity was not a problem; however, the limbs

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[3]With a 15% decrease in plasma volume and no decrease of red blood cell mass, hematocrit would rise to about 54%. However, a theoretical calculation shows that, due to the shape of the red blood cells, the maximum hematocrit that is theoretically possible is 58%, representing the most compact "packaging" of erythrocytes. Therefore, increase of hematocrit would greatly increase the viscosity of the blood without serving any obvious "purpose." Stated nonteleologically, it can be assumed that a mechanism has evolved for controlling the hematocrit at a constant level, leading to a decrease in red blood cell mass when plasma volume is reduced. As is known, the mechanism involved includes reduction of hemopoietic hormone production by the kidneys in response to increased oxygen delivery due to a tendency of the hematocrit to rise upon loss of plasma. Red blood cell destruction in the transient phase should also be expected.

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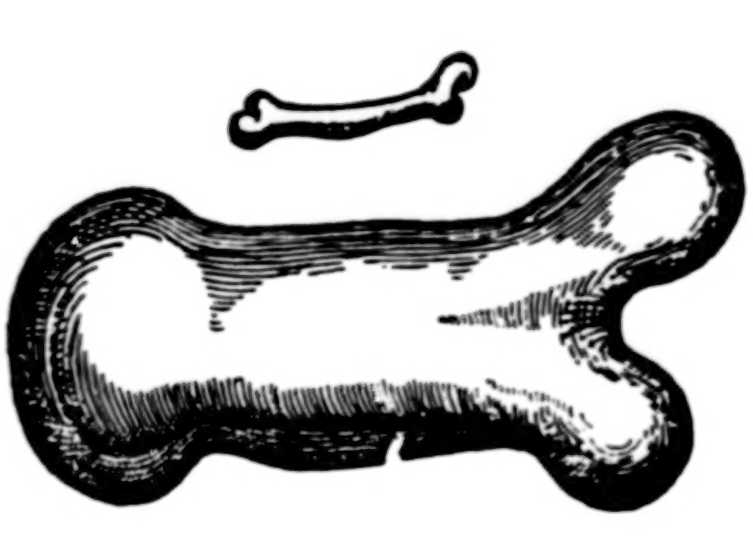

Figure 9.- Galileo's drawing of relative dimensions of a weight-bearing bone in a small and a large animal.

Figure 10.- Effect of increased gravity on bone diameter.

Figure 11.- Schematic illustration of the uncertainty in predicting the effect of extended exposure to weightlessness on the skeleton.

remained powerful (not much muscle was lost; as a matter of fact, it may have increased due to the need to move against water). Only so much bone was lost to make the remaining bone mass proportional to $BW^{1.0}$. This may be explained as follows: The sea mammals have to move in the water, which they accomplish by pushing away a water mass, the resistance to their movement being proportional to the cross section of their bodies, that is, to L^2. Further, hydrostatic pressure loads are proportional to body surface, that is, also to L^2. Therefore, it could be expected that they would need bones with cross section also proportional to L^2, that is, bone mass in this case would be proportional to body mass. (The last assertion follows from the fact that bone mass will be proportional to the product of length and

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cross section, that is, $L^2 \times L$ or L^3, and thus proportional to body volume and body mass.) Furthermore, sea mammals keep moving continuously in the water, and thus have enough exercise so that they do not face cardiac and muscular deconditioning.[4]

Heart Rate Increase

As used here, heart rate increase is a continuous elevation of heart rate and not the well-known reflex and temporary increase in response to emotional stress (see fig. 12). Increase of heart rate by 20% in Skylab 3 and 4 astronauts, both in

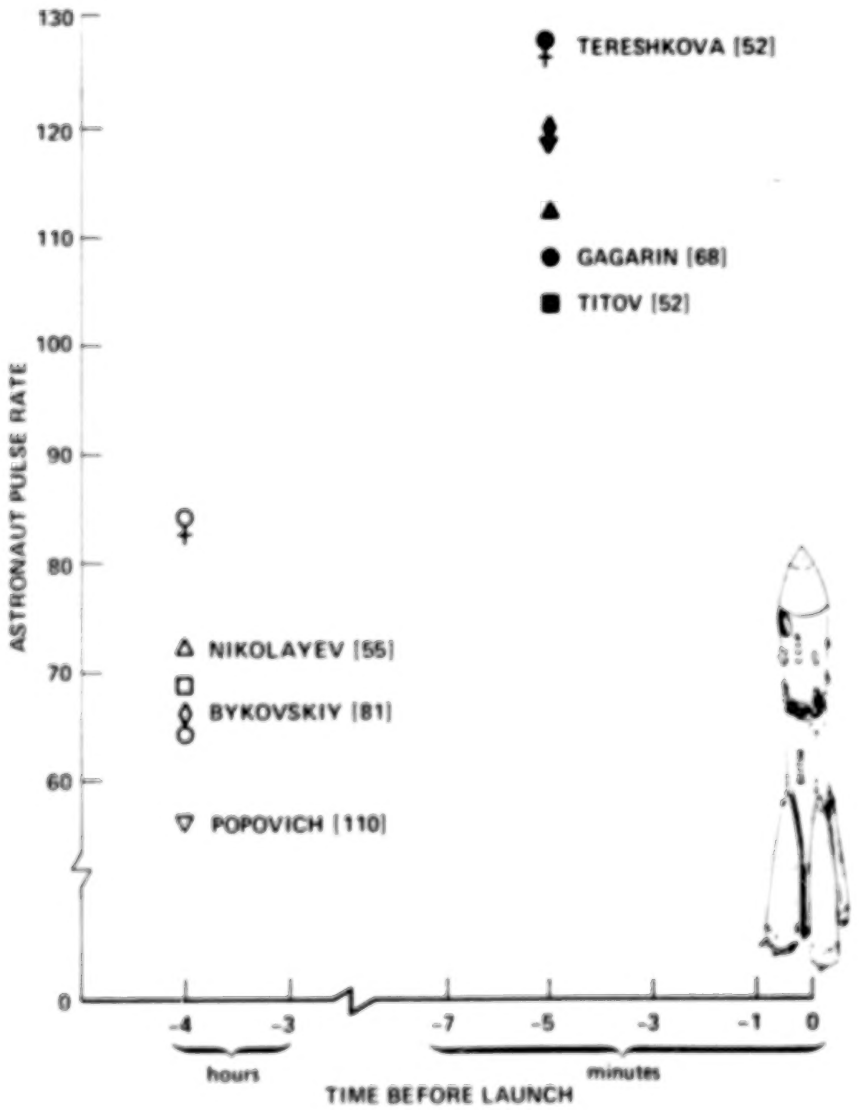

Figure 12.- Conditioned-reflex increase of pulse rate of Russian astronauts at launch (% increase in brackets). (Data from Parin et al., 1967: "Space Physiology")

[4]The principles of body scaling and the vertebrate body design are more extensively discussed elsewhere (A. C. Economos: On the Origin of Biological Similarity. J. Theor. Biol. 94: 25-60, 1982).

resting and stress conditions (exercise, lower body negative pressure), was considered as paradoxical and was not further analyzed in the literature. Since heart rate increase is apparently present from the first day in weightlessness, the above analysis suggests that it might be tied up with blood shifts in the first days in flight. That is, too much blood would be on the venous side of the heart, which should be pumped at a higher rate because cardiac output should not be increased, but reduced, due to a reduction of basal metabolic rate, as I argued earlier. An equivalent condition on Earth would be an experiment in which blood volume would be increased by external means. Search in the cardiovascular literature was instructive. I found that in 1915 Bainbridge reported tachycardia (increased heart rate) in dogs in which he injected blood or saline. This would then neatly explain Skylab 3 and 4 data. However, although for many years Bainbridge's observation was not challenged (it even became known as the "Bainbridge reflex"), others later reported bradycardia in response to experimental blood volume increases or even variable effects. Finally, it was demonstrated that if the basal heart rate of the animals was normal, the chance of a tachycardic response was high, but no response or sometimes bradycardia resulted if the basal rate was elevated before the experiment. At the present time I have no data on basal (preflight) heart rate of the Skylab 2 astronauts, but I would speculate that the many uncertainties associated with the fact that their flight was the first of its kind and the technical difficulties they knew beforehand they would encounter in the beginning of their mission, may have caused considerable and sustained emotional stress. Moreover, the high heat stress they were exposed to in the beginning may to some extent have provided a direct way of body fluid loss and have reduced fluid shifts to some extent. These two conditions may have prevented heart rate increase in flight in the Skylab 2 crew.

Body Weight Decrease

Fluid loss as an explanation of body weight loss was not considered adequate in the published report for, it was stated, it was "small" (of the order of roughly one liter). However, if the fluid and red cell losses calculated above are added, they give a figure of 1.5 liters. Now, 1.5 liters is 1.5 kg, which is not small compared with the 1-3 kg loss in body mass in flight. Another important consideration is that most of the astronauts lost weight also during the preparation period of 21 days prior to flight (particularly true for Skylab 2, where the loss was of the order of 2 kg). This would mean that the diet was deficient in calories for the activities of the astronauts on Earth; in weightlessness the deficit would be perhaps one-third less. Now, caloric intake was increased in Skylab 3 and 4, but so was exercise. At any rate, a proposed hypothesis in the published report that weightlessness had a high metabolic cost of unknown cause has not been rigorously tested. Only careful evaluation of the amount of work performed in space versus oxygen consumption for each astronaut would prove the assertion. Caloric intake is not a good variable to use in this respect because of the possibility of reduced efficiency of energy utilization and/or absorption by the gastrointestinal tract. An additional factor may involve the use of muscular power not usually expended for movement on Earth, where the feet touch the ground.

My analysis suggests that there is no apparent reason to doubt that the metabolic cost in weightlessness for the same activities (or no activity) as on Earth would be less, and probably is 20% less. (However, further investigations may show this to be not an accurate figure. For instance, it cannot be denied that some organs may have increased energy utilization in weightlessness to aid in the organism's efforts to adapt to this condition.)

BASAL METABOLIC RATE VS. BODY MASS: MAMMALS ARE NOT JUST "HEATERS"

Before attempting to summarize space-gerontological implications of the results of the systems synthesis I have presented, I would like to briefly discuss with you an important scientific question which is still unanswered although it is almost a century old, and which might be resolved by means of a space shuttle experiment.

During the first quarter of the 20th century, numerous empirical studies of basal metabolic rate (BMR) in various small mammals tended to confirm the theoretical notion that BMR is equal to the heat lost through the body surface ("surface law"). From this theory it follows directly that BMR would be proportional to $BW^{2/3}$ (BW = body weight, actually, body mass is understood here), because BMR would be proportional to surface or L^2 (L = a linear dimension of an animal's body), while BW is proportional to L^3. However, around 1930, Max Kleiber compiled data for a variety of mammals from mice to elephants, which indicated that $BMR = K.\ BW^{3/4}$, the "3/4-power law." The difference becomes significant when the ratio of the largest and smallest animals' body weights is above nine, and can be considerable when the ratio is very large, as shown by the following example. For a mouse BW = 35 g, while for a man BW = 70,000 g; therefore:

$$R = \frac{(BMR)\ man}{(BMR)\ mouse} = \left(\frac{(Bw)\ man}{(Bw)\ mouse}\right)^a = (2000)^a$$

If $a = 2/3$, then $R = 159$, but if $a = 3/4$, then $R = 299$; that is, $R_{2/3}$ is about 45% <u>less</u> than $R_{3/4}$.

In the last 10-15 years, measurements of BMR in mammals of the sea, mammals in the arctic cold, cold-blooded animals, and simple organisms have shown that the "3/4 power" law is roughly valid in them all. Irrespective of the value of the exponent, the fact that in <u>all</u> these species BMR increases slower than body weight cannot be explained at all with the original idea that mammals are a kind of heater, that is, they produce as much heat as they lose through their body surface. For instance, that idea predicted that BMR of animals living in the arctic cold would be elevated compared to similar animals living in more temperate climates. This is generally not true, certainly not when the magnitude of the temperature difference is taken into account. On the contrary, animals adapted to the arctic cold appear to be comfortable in that habitat (National Geographic movies). The low temperature has induced evolution of an effective body insulation (fur and adipose tissue). The same is true for mammals of the sea where, because of the greater heat conductivity of wet surfaces, the "evolutionary emphasis" has been on adipose tissue ("blubber") rather than on fur (no teleology here; it is simply that natural selection has favored this development). Sea mammals also make an extreme use of another beautiful mechanism to conserve body heat (we have it also in a small degree and arctic mammals to a higher degree). This refers to what is called "counter-current heat exchange" between the (warm) arterial blood toward the flippers and the (cold) venous blood returning to the heart, which is achieved by the contact of veins and arteries (which is the case in all mammals, particularly in their extremities). By this mechanism a large blood flow to the flippers is possible without loss of much heat.

The idea that animals are heaters originated from studies of mammals, which are warm-blooded and have an active thermoregulatory system to assure constant body temperature. Clearly, such a concept is not valid in cold-blooded animals which, ironically, differing from all other kinds of animals have a BMR-BW relationship that is closest to the theoretical relation $BMR = k.BW^{2/3}$ (predicted by the surface

law). An important and well-known observation in warm-blooded animals, when correctly interpreted, clearly suggests that even in these animals heat is not produced just because it is lost (which would be at any rate very belittling on living systems). This observation is simply that all mammals have a minimum metabolic rate in species-characteristic ambient temperature ranges. As a matter of fact, it is by definition the metabolic rate in such a "thermoneutral zone," as it is called, that is considered as the basal metabolic rate of an animal. Thus, at an ambient temperature lower than the lower limit of the thermoneutral zone, metabolic rate rises proportional to the temperature difference; in this case the animal's body is forced to increase its heat production to counteract heat losses in an effort to keep body temperature constant. (Note, however, that this is a short-term experiment. During long-term exposure to a low ambient temperature, the heat insulation system may adapt to a large extent to the new temperature, as in the case of arctic and sea mammals. That this capacity is inborn even in domesticated animals living at moderate temperatures was proved a century ago by Hoesslin, who raised two littermate dogs at 32°C and 5°C, and found that the dog at the low ambient temperature had a pelt 3.5 times as thick as his brother's, thus limiting the increase in his metabolic rate to only about 12% as compared with his brother.) What is even more interesting is that at an ambient temperature higher than the upper limit of the thermoneutral zone, metabolic rate is no more decreased despite the supposed decrease of thermostatic heat losses. It actually increases, as does body temperature, which indicates an inability to get rid of all the internally produced heat that is independent of heat losses. Even the metabolic rate of an animal starving to death behaves similarly in this respect.

I have, therefore, proposed the hypothesis that basal metabolic rate does not equal heat passively lost from the animal but heat actively produced by the cells of the animal in their function as thermodynamic machines, just because they are alive. Clearly then, the basal metabolic rate of an animal will be affected by its proportions of cells with various levels of metabolic activity. This alone would mean that larger terrestrial animals having a proportionally larger bone mass that is metabolically much less active than the other body cells would have a lower basal metabolic rate on a body weight basis.

If large and small animals were exact scale models of each other, then, theoretically, $BMR = k.BW^{1.0}$, which follows from the above reasoning. However, as we saw, Bone Mass = $k.BW^{1.15}$, which would transform the BMR-BW relationship into (roughly) $BMR = k.BW^{0.85}$. Since the established exponent is about 0.75, there is a difference of at least 0.1 that has to be explained. (This difference is on a percentage basis significant when animals with large differences in size are compared.)

It can be argued, however, that during the evolution of larger animals, BMR was reduced even more than a 0.85 exponent requires, because of constraints with respect to the necessity of losing the produced heat (which equals the basal metabolic rate). Now, heat is lost from a nonliving object at a rate proportional to its body surface, that is, $BW^{0.67}$. Clearly, evolution of terrestrial animals with an exponent lower than 0.85 and as close as possible to the theoretical minimum of 0.67 would be favored. On the other hand, the higher the exponent, the more active and productive the animal would be, which too, has a selective advantage. The exact exponent then will have evolved from an optimization with respect to these and perhaps some other constraints, particularly environmental conditions, characteristic of each taxon. (For a more general theory on the evolution of the scaling of basal metabolic rate, see: A. C. Economos, On the Origin of Biological Similarity, J. Theor. Biol. 94: 25-60, 1982.)

METABOLIC COST OF GRAVITY

It is from the present study of homeostasis in weightlessness that the idea arose that gravity may have played an important role in the evolution of terrestrial animals in this respect. Thus, we saw earlier that 20-30% of our basal metabolic energy may be expended for support of our form and posture in the Earth's gravitational field, even standing while performing no actual work. One can see this even more clearly by holding a heavy object in an extended hand — even though no gravitational work is performed, the muscles of the arm soon fatigue, which indicates increased metabolic work. Equally convincing is the observation that the basal metabolic rate of humans in the sitting posture is 10-15% higher than when lying relaxed, and 10-15% higher while standing rather than sitting, a total of 20-30% difference between lying and standing.

I do not want to pursue further at this time the evolutionary consequences of this observation.[5] A very interesting question, however, is what will happen in weightlessness. Thus, the metabolic cost of gravity for "similar" mammals is proportional to BW^a, where $0.85 < a \leq 1.0$ (since part of the bone mass will support itself statically without expenditure of energy). Therefore, if the gravity-related component of metabolic rate disappeared, BMR would be reduced and the exponent, which on Earth is equal to 0.75, would decrease. This is, then, a prediction that states that larger animals will be favored in weightlessness. It clearly constitutes a testable hypothesis.

I was able to derive an indication that this is probably a true hypothesis. The assumption is that under conditions of hypergravity (centrifugation), an opposite situation would exist, namely the larger animals would be at disadvantage (i.e., they would have a higher increase of metabolic rate per gram of body mass); in other words, exponent a would now increase as compared to its value in the 1-g environment. Such an increase in specific metabolic rate of the whole animal would be to some extent reflected also in an increase in specific metabolic rate of tissues of the animal in vitro. That this is so is supported by published data (Daliggon and Oyama, 1975) on glucose metabolism by diaphragm tissue obtained from chronically centrifuged rats (fig. 13). A fact well known from metabolic studies (which I have also observed in my studies of exercising rats) is that specific tissue metabolism and whole animal BMR are reduced with increasing body weight (age) in normal gravity and within one species, due to increasing hypodynamia with age and to decreasing ratio of metabolically active versus inactive tissue, as well as decreasing ratio of body surface to body weight (reduced efficiency of necessary heat loss). In addition, an aging-related mechanism may be involved. A linear log-log relation for

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[5]Only a single speculation will be mentioned here. The above analysis of the large metabolic cost of gravity stimulated the following interesting observation. It is clearly generally true that poikilothermic animals of the land are as short-legged as possible (e.g., snakes, lizards, turtles, etc.). Since heat losses and metabolic rate in these animals may be five or more times lower than in homeotherms of equal weight, a high-standing terrestrial poikilotherm would expend too much energy in support of posture compared to its basal needs, a trait not favored by natural selection. The case of the dinosaurs is intriguing. Were they cold-blooded? In that case, being so huge, they would be very inefficient "machines" having to waste so much energy against gravity. So, possibly, most of them were warm-blooded.

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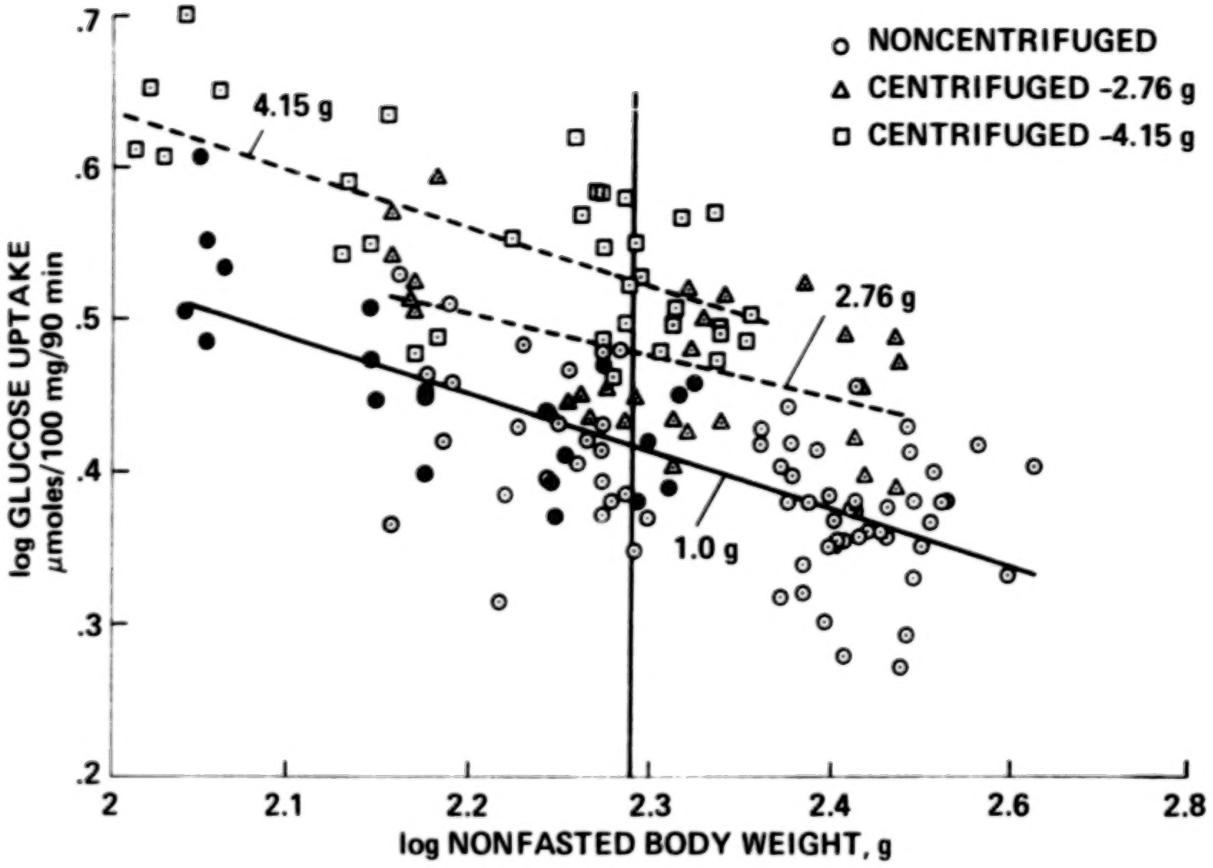

Figure 13.- Relationship between glucose uptake rate by rat diaphragm in vitro and body weight after long-term exposure to various levels of simulated increased gravity. (Redrawn from Daliggon and Oyama, 1975.)

tissue metabolism versus body weight in normal gravity is thus well established and also found by Daliggon and Oyama for glucose uptake by diaphragm tissue. In hypergravity, then, my hypothesis implies that the slope of this linear log-log relationship would be less than in normal gravity (large animals would have larger increases of their metabolism than smaller animals). This is indeed the case for 2.76-g. In the case of 4.15-g, the change of slope is not apparent; a reason for this might be possible interference of other factors due possibly to a too large deviation from normal conditions. However, I believe that the main reason is the inclusion in the curve of very small – and thus very young – animals, so that growth effects and interference cannot be excluded. Probably the log-log linear relationship does not hold for very young (small) animals. For example, from the table on which the figure was based, one gets for 80-g control rats a value of log glucose uptake equal to 0.82 which is much higher than the extrapolated value from the figure (falls outside the body weight scale). Nevertheless, the point for 108-g rats at 4.15 was included, and this has probably biased the regression line considerably in this case. If one ignored that point, since the point for 80-g controls was also ignored, then the regression line would be almost horizontal, which would be in good quantitative agreement with the reduction of slope from 1-g to 2.76-g and the hypothesis proposed here. (Note: This different interpretation of the data in no way affects the authors' interpretation and conclusions, which were unrelated to the present discussion and centered around showing an increased glucose metabolism in centrifuged rats as compared to body mass-matched controls at normal gravity.)

Therefore, it is expected that the exponent will be less than 0.75 in weightlessness; a space experiment can thus contribute to the resolution of an outstanding scientific problem.

LONG-TERM EFFECTS OF WEIGHTLESSNESS — GERONTOLOGICAL IMPLICATIONS

Metabolically speaking, then, living in weightlessness would be beneficial and the aging rate could be expected to decrease. However, the astronaut's head would have too much blood permanently, although some adaptation may occur. The only countermeasure to head fullness that was very effective in previous spaceflights was exercise, but perhaps so much exercise is needed that the metabolic cost of weightlessness may become even higher than on Earth! Lower body negative pressure may be equally inadequate as a countermeasure because of difficulties it causes to the obligatorily deconditioned cardiovascular system; moreover, while preventing the deconditioning it almost by definition may increase the metabolic cost to Earth levels. A problem of grave concern should be the skeleton. The forces on the bones during movement or activities in space are much smaller than those on Earth and bone will keep being lost until the skeleton's strength becomes commensurate to the loads (as in the case of sea mammals). Again, increasing the load may increase the metabolic cost. If the astronauts would never return to Earth, they would have no problems from bone loss; their skeletons would not fail them in weightlessness (this is, I believe, precluded by the evolutionary programming as sketched above). But bone strength may be reduced so much over long-duration flights that the bones would not be able to withstand gravity and reentry accelerations. Finally, loss of muscle can be analyzed similarly. Therefore, a small (10-15%) slowing down of aging rate of humans who would not care to return could be expected, with some uncertainty about the long-term effects of head fullness on mental capacity and body homeostasis (the latter through effects on the hypothalamus).

Regarding the confidence limits of this last hypothesis of reduced aging rate in weightlessness, I am concerned particularly about the possibly increased "rate of living" of specific organs of the body involved in establishing a new "adapted" state of the body in weightlessness. What is, for instance, the effect on the kidney of increased urine production (if it is permanent) or of continuous calcium loss (increased danger of kidney stone formation?). An even more serious concern is the following: if heart rate would not return to preflight values during long-term exposure to weightlessness, this would certainly constitute a burden for the heart, which, therefore, might age faster in space than on Earth. (Note that the simultaneous reduction in cardiac output will have only a small alleviating effect, because mechanical output of the heart is usually only 5-10% of its total energy input. This striking low efficiency of the heart as a thermodynamic machine may be the secret of its longevity. It could be assumed that the remaining 90% of the energy utilized by the heart is directed toward mechanisms of "counterentropic metabolism" that repair "thermodynamic" damage continuously inflicted on heart cells during their metabolic function, i.e., their "staying alive" and producing the required mechanical work.) Such considerations of effects of weightlessness on specific organs suggest that the total effect of weightlessness on an astronaut or space traveler will depend on the functional state of his various organs and organ systems, which taken together in an integrated manner, represent the individual's "biological age."

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METABOLIC EFFECTS OF HYPERGRAVITY ON EXPERIMENTAL ANIMALS

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My research has been concerned with exposure of animals, ranging in size from rats to dogs, to acute or chronic centrifugation. Table I shows the various physiological parameters that we have measured during the acute stress response of animals to centrifugation and the parameters investigated with respect to long-term adaptation to hypergravity. Later, I will comment on some of our observations that may be relevant to the research on aging.

TABLE I.- GRAVITATIONAL RESEARCH PROGRAM

ACUTE EXPOSURE STUDIES	CHRONIC-LONG TERM EXPOSURE STUDIES
PHYSIOLOGIC STRESS MONITORING	PHYSIOLOGIC ADAPTATION
BODY TEMPERATURE	BIORHYTHMS-TEMPERATURE-HEART RATE
HEART RATE	METABOLIC RATE
OXYGEN CONSUMPTION	ENDOCRINE FUNCTION
CARBON DIOXIDE PRODUCTION	GROWTH & DEVELOPMENT
FOOD CONSUMPTION	BODY COMPOSITION
HYPOTHALAMIC-PITUITARY-ADRENAL FUNCTION	MUSCLE & BONE
BLOOD GLUCOSE HOMEOSTASIS-INSULIN	INTERMIDIARY METABOLISM-GLUCOSE
GLUCOSE METABOLISM-LIVER-MUSCLE-BRAIN	REPRODUCTION
	PHYSICAL ACTIVITY

Table II shows the physical effects of exposure to hypergravity. As you can see, there are changes in hydrostatic pressure gradients, fluid distribution, weight, size, shape and position of organs and, of course, an alteration in the gravity receptor system. These physical changes, which are induced by hypergravity and are transduced and amplified by the CNS and the neuroendocrine system, can affect practically all the physiologic, metabolic, morphological, and behavioral parameters of the animal.

Figure 1 documents the differential growth response of rats under chronic centrifugation. This experiment was performed on animals that weighed at weaning age from 80 to 90 g. They were placed on a 12-ft radius centrifuge operating at 30.5 rpm and exposed to two different g levels, 2.76-g and 4.15-g. Some deaths occurred early during centrifugation, which cannot be attributed to hypergravity exposure per se. Apparently, some of the recently weaned rats were caught in the wire mesh screen floor of the cages and died. The main finding in this experiment was that the growth

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TABLE II.- VERTEBRATE ORGANISM RESPONSE TO GRAVITATIONAL CHANGE

G-CHANGE EFFECTS ON	MECHANOELECTRICAL TRANSDUCTION	BRAIN – CNS SYSTEM	RESPONSE SYSTEM
WEIGHT/MASS RELATIONSHIPS	PRESSURE RECEPTORS	NERVOUS SYSTEM	STRUCTURAL MORPHOLOGICAL COMPOSITIONAL
HYDROSTATIC PRESSURE GRADIENTS	STRETCH RECEPTORS	NEUROENDOCRINE SYSTEM	FUNCTIONAL
BODY FLUID DISTRIBUTION	CHEMORECEPTORS	ENDOCRINE SYSTEM	PHYSIOLOGICAL METABOLIC BEHAVIORAL
ORGAN/TISSUE SIZE, FORM, POSITION	VESTIBULAR RECEPTORS	HORMONES	

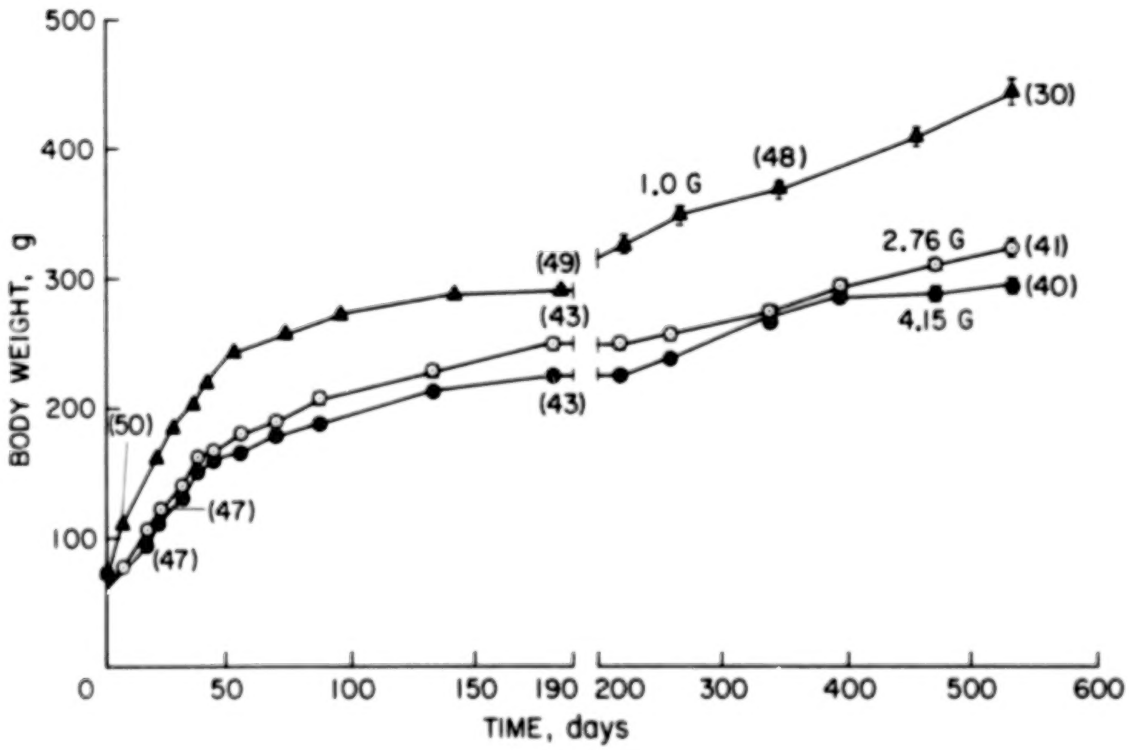

Figure 1.- Growth of female rats exposed to chronic centrifugation.

rate was depressed in inverse relationship to g. We continued the study up to 525 d, and the data showed that the difference in body size between control and centrifuged rats was maintained throughout the entire centrifugation period. Our observations also showed that the higher the g-intensity, the smaller the body size that the animals attained.

Figure 2 deals with a similar study that lasted for 182 d. In this particular study, young male beagle dogs were used. The animals were about three months old and weighed approximately 5 kg at the initiation of the experiment. For the first 10 days of centrifugation, we increased the g field gradually, reaching a final g level of 2.6 at the outermost position of the centrifuge (position 2, approximately 20-ft radius). The animals showed an initial stress reaction, manifested by

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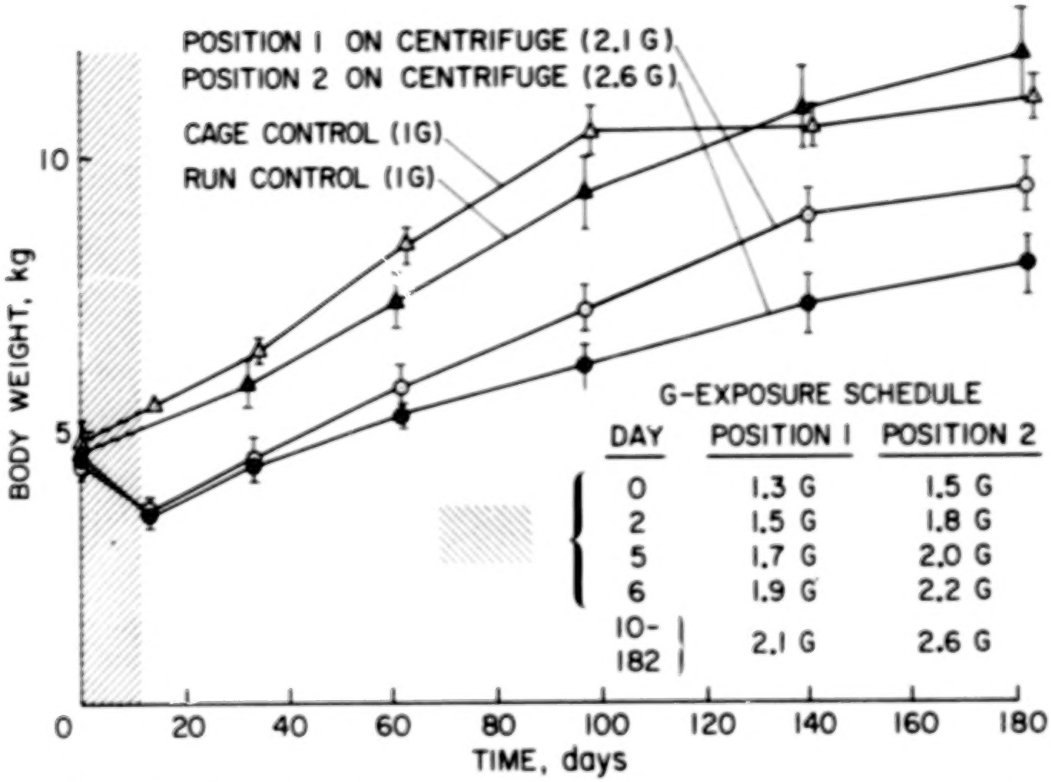

Figure 2.- Growth of beagle dogs under normal and hypergravity conditions (six dogs/group).

decreased food intake and body weight loss. Afterwards, the dogs seemed to recover, but their growth rate still was lower than that for control animals. As in the case of the rats, the body weight attained at maturity was significantly lower than for the noncentrifuged animals.

The above effects on growth rate and body weight have also been documented in centrifuged mice and hamsters. We believe, therefore, that these effects represent a generalized response to hypergravity.

Figure 3 illustrates the fact that both male and female rats show the effects on body weight.

Figure 4 deals with the metabolism of the rats. It shows the curve plot of the resting metabolic rate of the animals under normal gravity and is a regression of the O_2 consumption as a function of body weight. Instead of the 0.75 regression coefficient value shown by Kleiber for mammals, we have obtained a mean regression coefficient value of 0.45 from 2 wk to 1 yr old rats. The data show that at any given weight, for instance 300 g of body weight, the metabolic rate of the centrifuged animals is about 20% higher than that of the controls. Thus, it seems that hypergravity induces a significant increase in metabolic rate. We use a 4-ft radius metabolic centrifuge for these measurements. The animals are first adapted to hypergravity on a 12-ft radius centrifuge and then transferred to the smaller centrifuge for the respiration studies. In some experiments, we have stopped the metabolic centrifuge and measured the O_2 consumption of the animals during the first 2 hr of deceleration. Our observations suggest that there was essentially no change in respiration during the 2 hr after the centrifuge was stopped. At 24 hr after return to 1-g, the resting metabolic rate had fallen to about 25% of the values shown by rats adapted to hypergravity and remained low over the next 22 d during which the animals were investigated.

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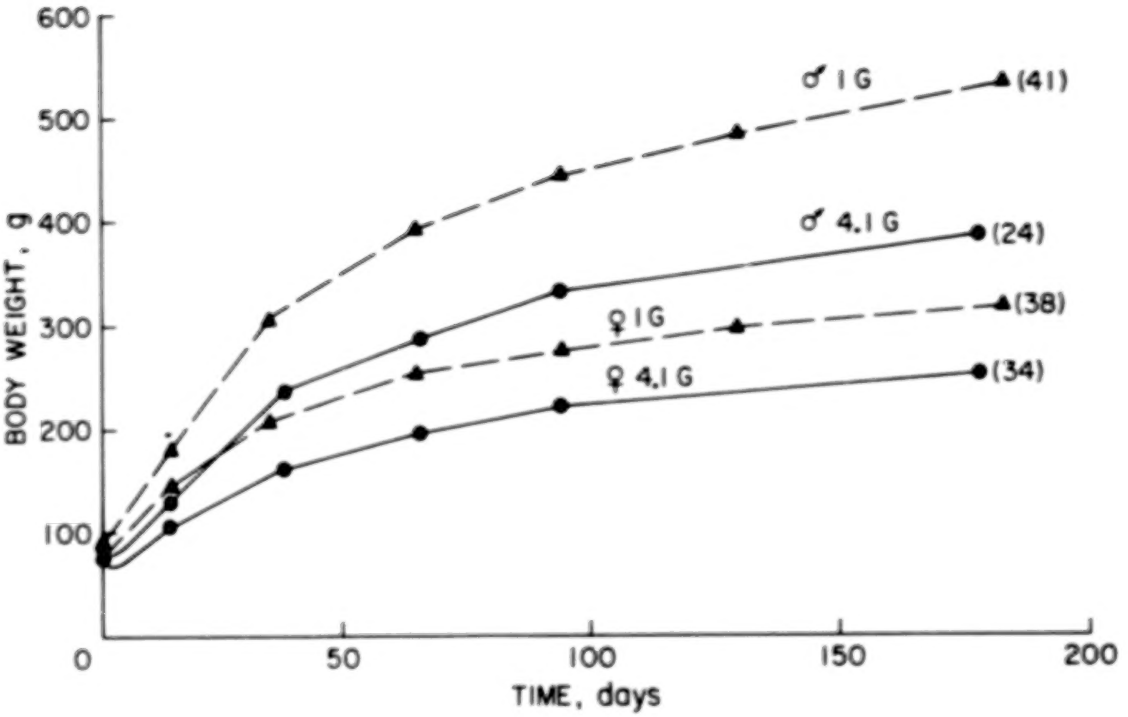

Figure 3.- Growth of male and female weanling rats under normal and hyper-g conditions.

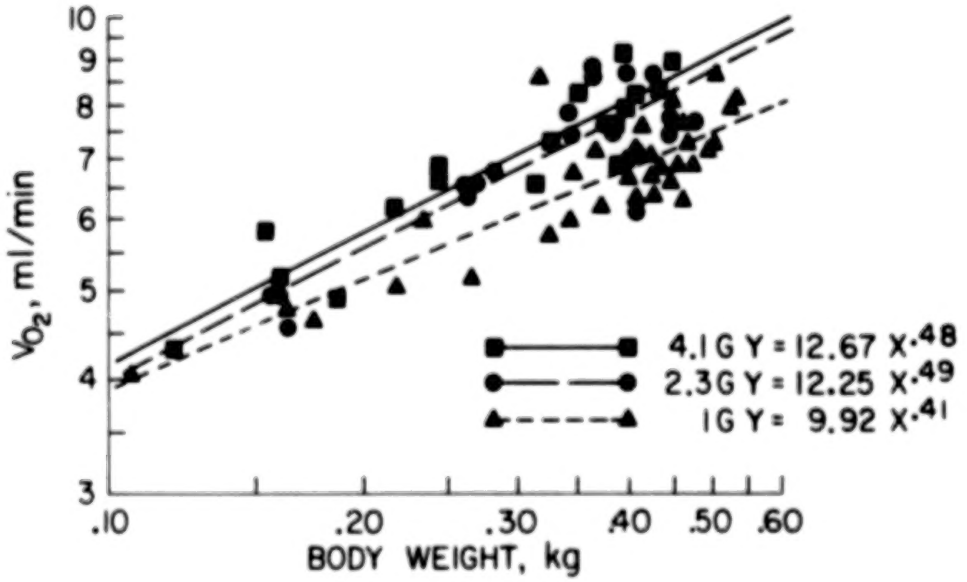

Figure 4.- Log-log regression of O_2 consumption on body weight of normal and chronically centrifuged rats

There was a small body weight increase in a few of the animals, but not much in those animals that had been on the centrifuge for one year.

Figure 5 relates to the metabolism of animals adapted to hypergravity and the results of an oral glucose tolerance test performed on the rats. The animals were administered 300 mg of glucose per 100 g of body weight per os; then we measured the

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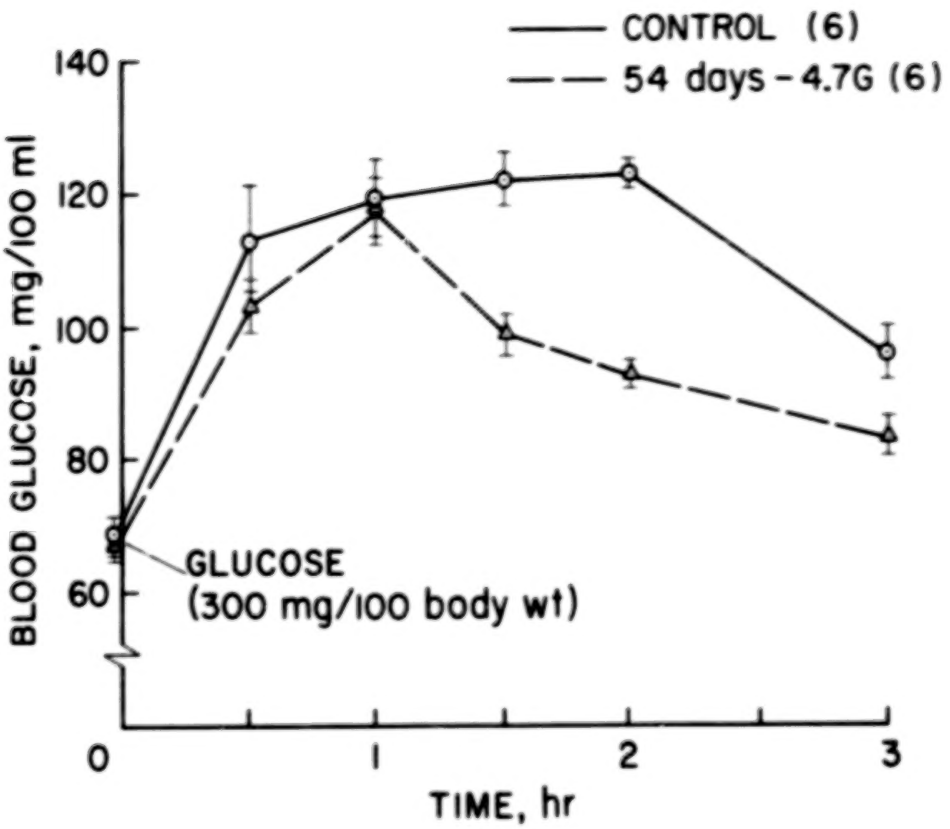

Figure 5.- Oral glucose tolerance of centrifuged rats.

subsequent rise and fall in blood sugar level. The animals centrifuged for 54 d at 4.7-g showed a faster rate of glucose removal. This is in agreement with the fact that the centrifuged rats have a higher metabolic rate and may have some implications regarding the probable accelerated aging of animals exposed to chronic centrifugation.

Figure 6 illustrates the effects of prolonged physical loading. It shows that exposure of rats either to 3.6-g for 21 m or 4.7-g for 25 m induces a very marked deformation of the vertebra of the thoracic cervical region.

Figure 7 shows the general appearance of the centrifuged rats. They look quite normal except for the fact that they have coarser hair and are definitely smaller than the controls. Our more recent studies show a distinct sagging of the skin of the rats at exposure times of 18 m or longer in the centrifuge.

During the first week of exposure, the animals show a typical head nystagmus response when we stop the centrifuge. This is a sign of perturbation of the semicircular canals of the inner ear. This response fades after 7 to 14 d. Afterwards, their vestibular systems appear to be desensitized to abnormal motions. This is suggested by our observation that animals maintained at high g have a higher threshold to motion changes.

Another effect of chronic centrifugation is the loss of body fat (figs. 8 and 9). Drs. Arthur Smith and Nello Pace have exposed primates to hypergravity (2.5-g) for several months at the University of California, Davis. They measured the fat deposits by an indirect procedure; according to their data, the centrifuged animals had a higher accumulation of fat. Apparently this is the only exception,

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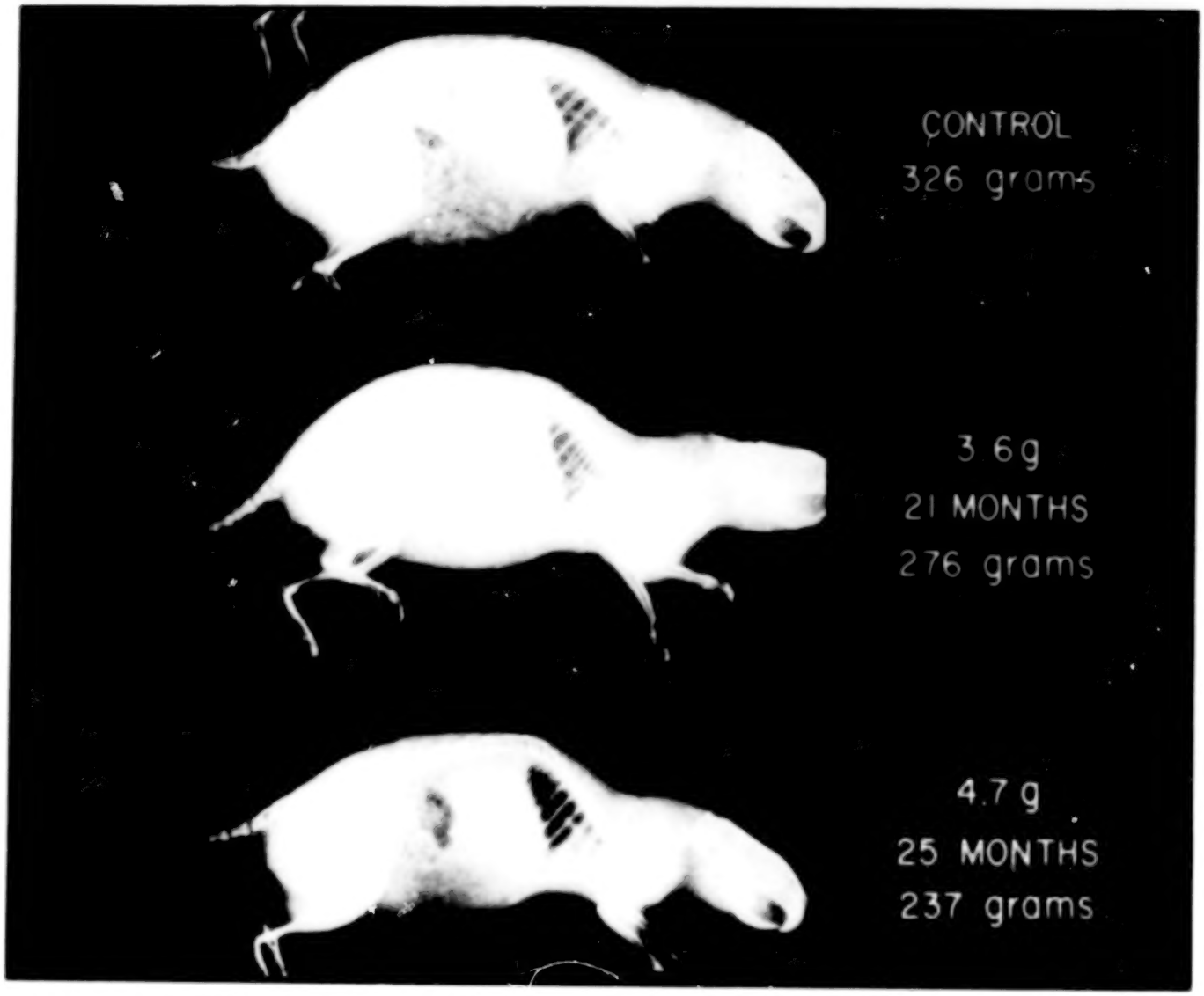

Figure 6.- Radiograph of vertebral column of a chronically centrifuged rat showing marked lordosis.

since data from other laboratories has shown fat l[illegible]n all other species of animals exposed to hypergravity.

Figure 10 shows the centrifuge used in our present experiments. It has a 25-ft radius and is adequate for studying the chronic effects of hypergravity on animals as large as beagle dogs. Presently we are studying the effects of high g on the bone density of dogs. In the near future we believe we will be able to operate this centrifuge without interruption for periods as long as 6 m.

Regarding the aging process, we have observed an apparent age-related mortality starting at about 18 m of age. As indicated above, any earlier deaths may be accidental due to the fact that some animals are trapped on the wire mesh screen.

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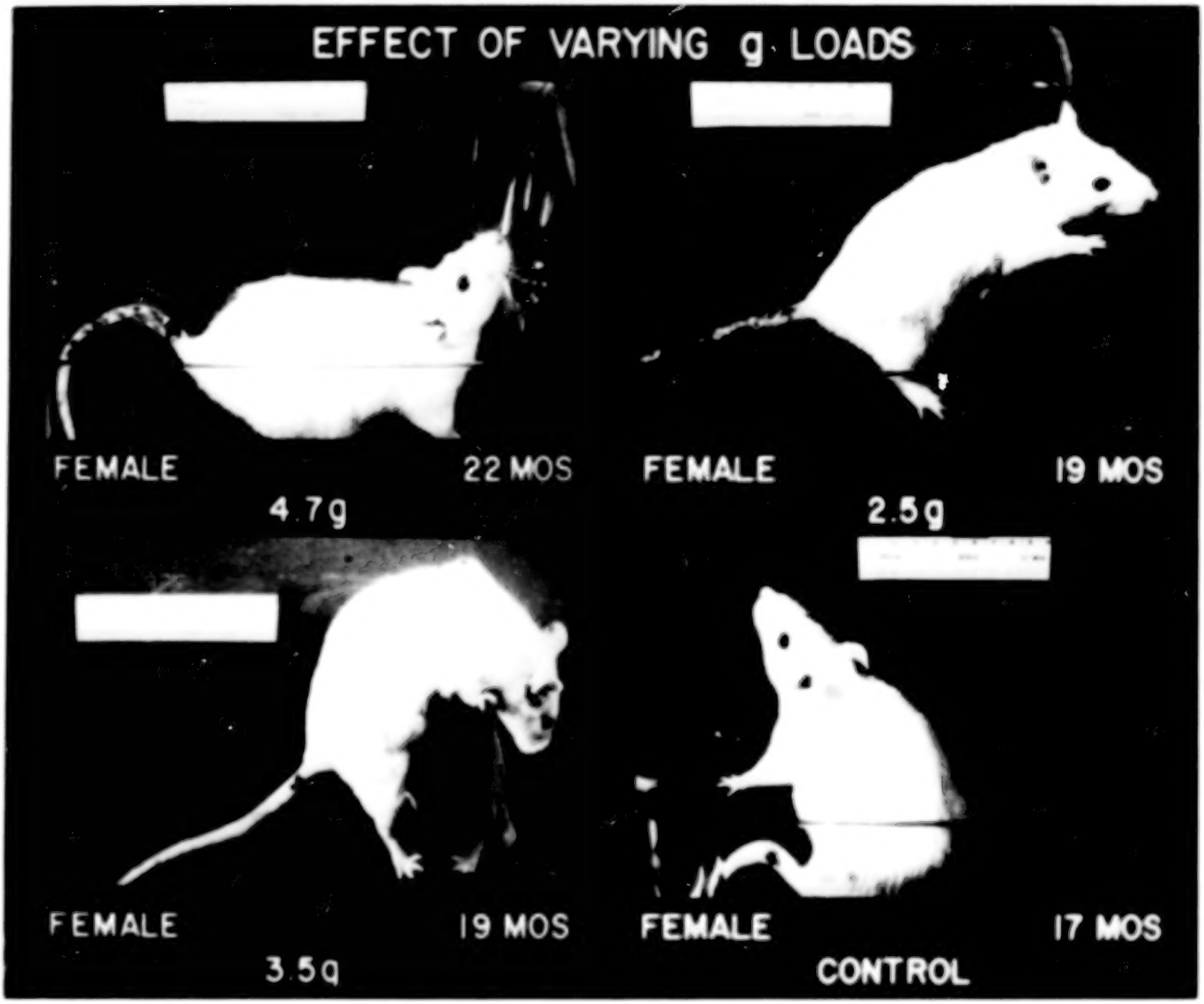

Figure 7.- Effect of varying g loads on gross appearance of chronically centrifuged female rats.

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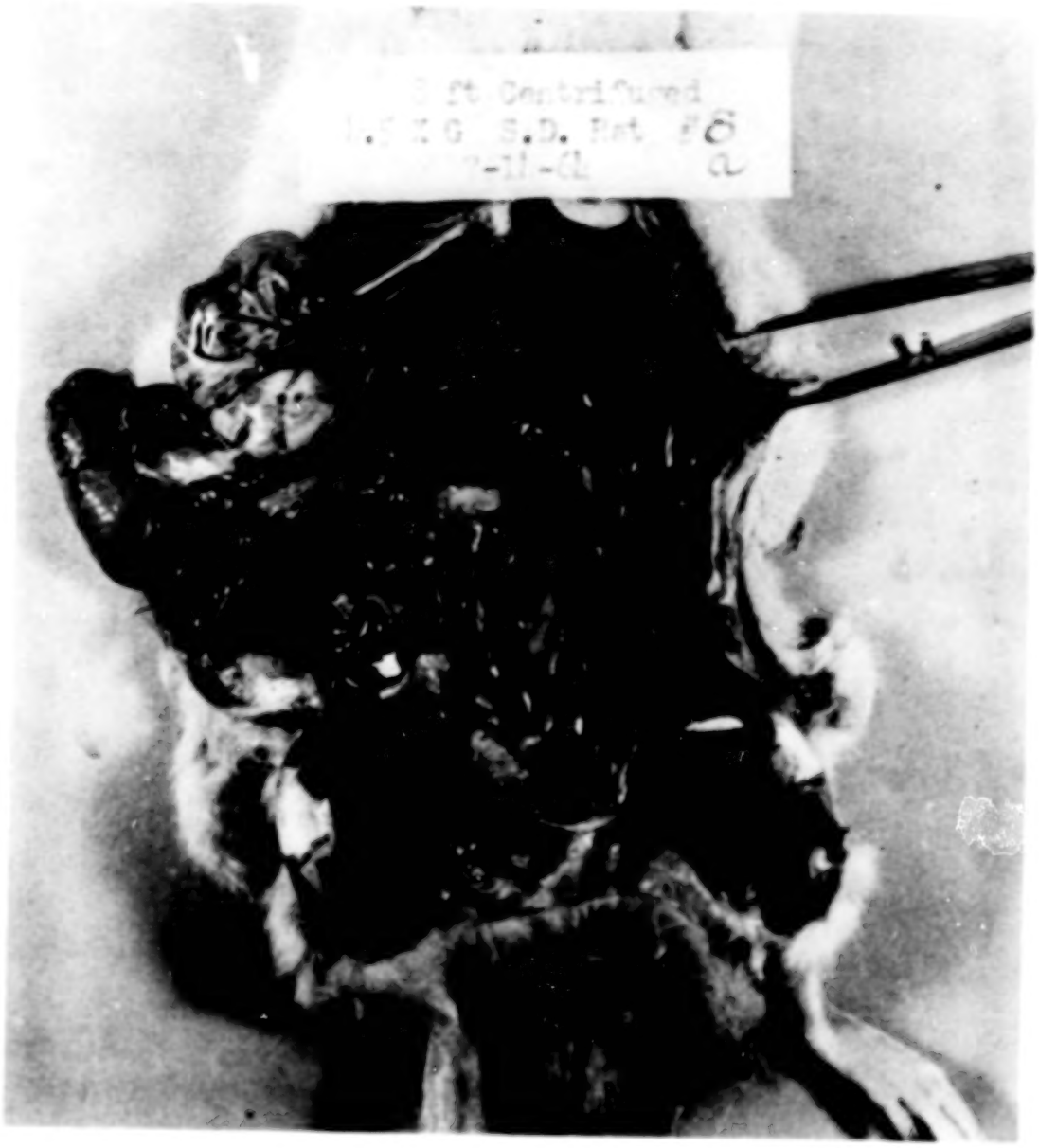

Figure 8.- Abdominal cavity showing absence of fat in a rat that had been exposed to 4.5-g for 1 yr.

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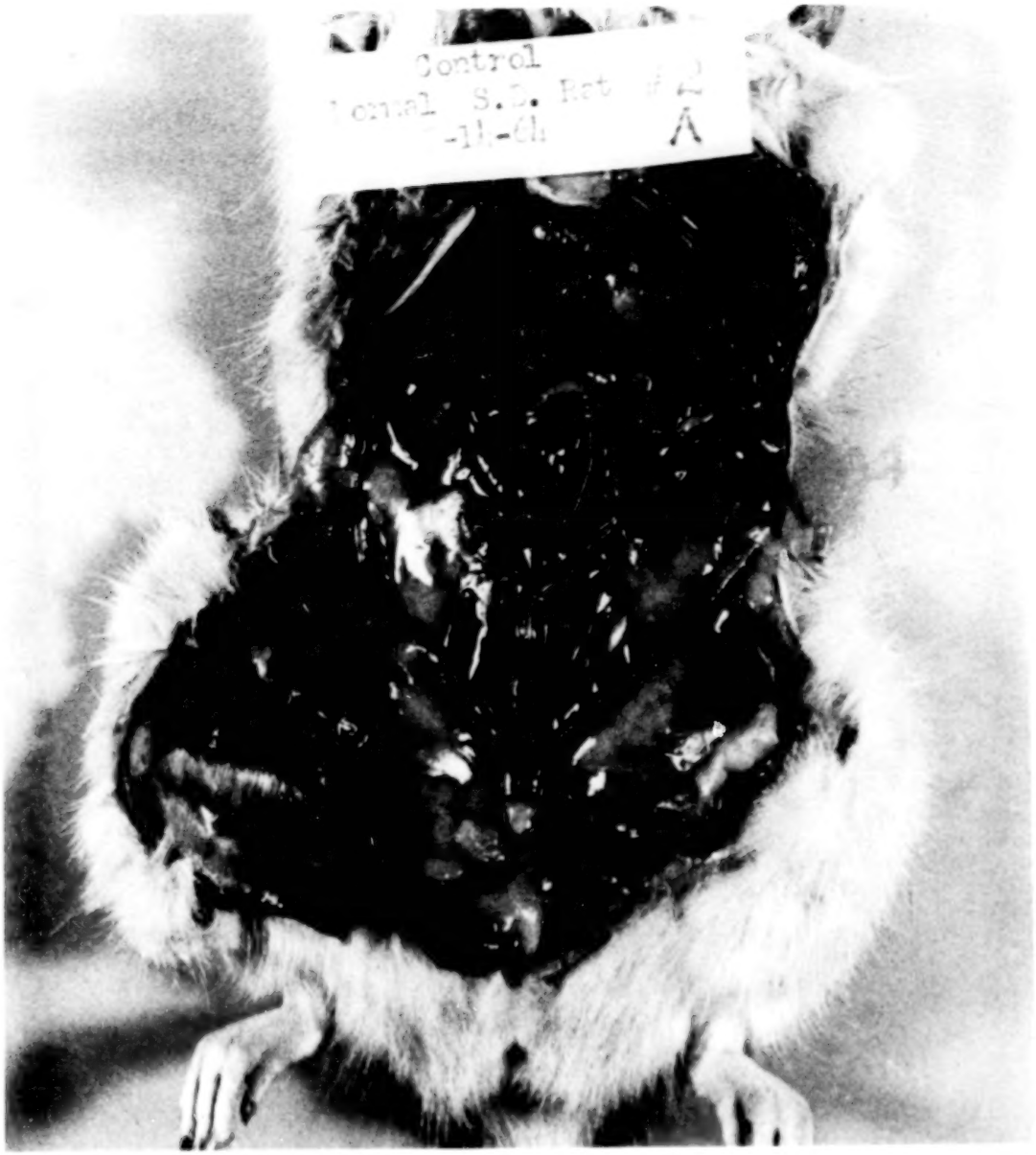

Figure 9.- Control rat showing a normal amount of fat in the abdominal cavity.

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Figure 10.- Ames Research Center 20-ft radius centrifuge.

DISCUSSION

COMFORT: I believe that you mentioned that you stop the centrifuge to service the cages, so the animals are not deprived of all experience of normal gravity.

OYAMA: This is correct. We also have a 52-ft diameter centrifuge that enables us to run continuously without any stoppage whatsoever, because it has an automated waste system. I have determined the growth curves of weanling rats that were on this centrifuge for at least 2 m nonstop and, although the growth curves were generally measured at a lower level than those on the nonautomated centrifuge, in one case where a comparable g intensity was used, the growth curves could almost be superimposed. Thus, we do not feel that the half-hour, twice-a-week stoppage has a significant effect on the overall growth patterns of these animals.

COMFORT: This morning Dr. Bensch talked about cells which may not "exercise" at all in weightlessness, and we are dealing here with a system which perhaps allows the overstimulation of those very same cells.

OYAMA: We have made some preliminary studies looking at the free-running activity of these animals using a little circular wheel. During the early stages of exposure to hypergravity when they are under stress (at both low and high g levels) and for a considerable period thereafter (at the higher g levels only) nocturnal running activity is severely curtailed. They are truly inactive at the higher g levels. No data have yet been obtained on the running activity of hyper-g-adapted animals, that is, those which have been on the centrifuge for several months.

SACHER: With respect to those animals that have been exposed to hyper-g during growth and reached a different body weight, what is their subsequent mortality compared to controls which get much larger?

OYAMA: Unfortunately, we have not done a significant study on the aging process of these animals. However, we did an experiment in which the animals were centrifuged until they reached almost 100% mortality. There is no doubt in my mind that under hyper-g conditions the maximum life span of the rats is shortened, as compared to the controls. The actual data show that we started with about 50 animals, maintained at the highest g level (i.e., 4.1-g) almost 2 years ago, and now there is just one survivor in the centrifuged group in contrast to a considerable number of controls.

SACHER: I gather that experiment protocols are being considered that involve growing animals at zero-g to be observed thereafter. The analogous experiment would be like yours where they are kept at hyper-g for a month, during their growth period, and then they are followed thereafter.

SHOCK: These animals, after they came off the centrifuge, did they show any additional growth? Could they reach, at 1-g, the weight characteristic of the control, noncentrifuged animals?

OYAMA: It just depends on the exposure time. If you expose weanling animals and allow them to grow on the centrifuge for say 3 months and then you stop centrifugation, they drink a lot of water, so they behave like dehydrated animals. They also eat a lot and, thus, they show a spurt in body weight gain, but a normal body weight is not reached unless the animals are left at 1-g for a long time. On the

other hand, animals that have been exposed to high g for one year show no change whatsoever in normal weight when they return to normal gravity, and they remain permanently smaller than the controls.

MIQUEL: Have you checked the organ to body weight ratios? I wonder if the lordosis induced by high g influences the weight of some organs by restraining their growth.

OYAMA: I recall that there was a significantly higher liver-to-body mass ratio. At the highest g level (4.7-g) we saw also a marked absence of body fat.

SAMORAJSKI: Do you use mature or old animals?

OYAMA: We routinely use both, but in our chronic studies we usually start with weanling animals. I have presently a colony of second generation rats that were conceived and reared on the centrifuge and have been subjected to the twice-a-week stoppage. They can mate and reproduce at 2.0- to 2.3-g's.

ECONOMOS: Is the food intake increased in these animals despite the fact that they do not grow as much as the controls?

OYAMA: The food consumption of the rats maintained at high g is equal to or higher than for control animals when expressed in terms of the absolute amount per day, per animal. Since the centrifuged animals are smaller, if we consider the food intake consumption per unit of body mass, there is a very significant increase in food intake in the centrifuge of about 10 to 20%.

KRAFT: You have mentioned the effects on growth. Could it possibly be the quality of the food that might be a limiting factor in the centrifuge conditions? Perhaps if they were given vitamin, mineral, and fatty acid supplements while they were being centrifuged they would grow normally.

OYAMA: We use in all our experiments Wayne Chow, both for the controls and for the high-g animals.

COMFORT: The rebound after readaptation to normal feeding of calorically restricted rats goes on for at least a year and a half or 2 years. I wonder if you have looked at occipital closure or have any evidence that under hypergravity the growth of the rat is terminated earlier?

OYAMA: We have not investigated occipital closure and have no evidence that growth is terminated earlier on the centrifuge. Dr. Antmann, from Hannover, Germany, with whom I am collaborating, has run some studies on bone density and structural changes in rats that have been exposed to high g for a number of months or years and has found an increase in bone density. Moreover, the structure of the bone suggests there is more resistance to loading in the centrifuged than in the control animals. These changes are much easier to demonstrate in the dog, which, as could be expected, is a better model than the rat because of its size and other anatomical characteristics. Thus, in dogs we find that hypergravity induces hypertrophy and density distribution changes in the radius.

MEITES: Is there any change in intestinal transport time at the high g levels?

OYAMA: I believe that Dr. Pitts has shown that rats exposed to high g appear not to have a different rate of absorption of food.

MIQUEL: I am very intrigued by your finding of a smaller size in the rats which have developed in the centrifuge. This reminds me of the work of Dr. David from Lyon, France, on the effects of temperature on the development of Drosophila. This work has shown that flies raised at relatively higher temperatures use more O_2 and develop faster. On the other hand, their final size is smaller than for their counterparts maintained at lower temperatures. What is interesting from a gerontological viewpoint is that the flies which developed faster did not live as long as the controls when both groups were maintained afterwards at the same temperature. This suggests that, at least in insects, factors which influence development modulate the duration of adult life even though longevity is fundamentally preset by genetic specifications. Similarly, the longevity of rats raised in the centrifuge may be affected, in view of the effects on growth described by Dr. Oyama. I believe that this is an area in which gravitational research could contribute important information on mechanisms controlling the rate of aging.

MEITES: What happens to reproductive function in the female rats? Does anything happen to the estrous cycle?

OYAMA: No, so far as I know. In our studies we take animals that have been in the centrifuge at 2.3-g from 2 to 3 m and when the male and the female have been left together the delivery takes place in 21 or 22 d. Therefore, the estrous cycle is not apparently altered.

Occasionally, there is a lack of conception, but we have seen many successful pregnancies. At the highest level of gravity used by us, that is, 4.1-g, there is no conception, and we believe that this is because of testicular atrophy and other changes in endocrine function. As a matter of fact, our histological studies have documented testicular atrophy in rats exposed to 4.1-g. However, at 3.5-g the rats can mate and the pregnant females have successful deliveries. The young rats survive for maybe one day, but then death occurs. At 2.5-g we have been able to obtain the survival of one litter and at 2.3-g about 50% of the litters survive. Animals that have mated and successfully raised their litter at 2.3-g can reproduce afterwards with no problem. However, the naive rats are not so successful. It seems that the critical part is nursing and if a female can nurse her young in an experiment at 2.3-g, she will be able to reproduce successfully in subsequent matings. This has allowed us to perform multigeneration studies.

COMFORT: Assuming the hypothalamus is weighing the body weight, centrifugation could be expected to increase the lifespan in the same way as caloric restriction, because the hypothalamus is reading the food intake as small versus the apparent mass.

OYAMA: The mass of the animals in the centrifuge is small, but their weight is doubled or tripled because of the increased g fields. On Earth we use weight and mass as equivalent and interchangeable terms. Hopefully, we may be able to develop a metabolic rate function which includes both the animal mass and the weight as separate variables. Thus, in weightlessness, where g is zero, one can determine the true resting metabolic rate of an animal that is due to its mass function alone.

MIQUEL: In a gerontological context, I find most interesting that we may be able to translate environmental inputs such as ambient temperature and g forces into

oxygen consumption. It is most likely that any environmental change away from the optimum level carries a price in terms of the increased oxygen utilization required to produce the higher quotas of energy needed to survive in a more stressful environment. This, in turn, according to the free radical theory of aging, may result in premature senescence. In agreement with the above ideas, if centrifugation induces an increased respiration rate, the centrifuged animals should not live as long as the controls.

SACHER: Getting back to the centrifugation program, it seems that the g's used are so high that an asymptote has been reached. If you want to look at functional dependence, you are going to have to go down to the range between 1- and 2.5-g.

OYAMA: On our 25-ft radius centrifuge we did some growth studies in rats at about 3/10 of 1-g increments, that is, at 1.3-, 1.6-, and 1.9-g, and we saw a very clear rectilinear relationship between growth and g intensity. Thus, the rats could distinguish the 3/10-g increment as shown by the average maximum body weight attained.

SAMORAJSKI: Have you done any biorhythm measurements?

OYAMA: Yes, we have the capability of measuring heart rate and core body temperature by implanted telemetry. Our analysis, for example, on rats exposed to chronic centrifugation at 4-g reveals that the temperature biorhythm does not return to the prestress level until after 3 w of exposure. We have found similar effects in dogs. Usually the biorhythm pattern is extinguished — flattened out. There is almost no detectable periodicity, but then it does come back slowly at a rate which depends on the g intensity. We consider that, in terms of physiologic adaptation, the temperature and heart rate biorhythms are among the most reliable indices of physiologic adaptation. Thus, acutely stressed rats and young beagle dogs show a rapid and profound decrease in body temperature (up to 4-5°C) within the first hour of centrifugation. It takes up to 3 d for the return of the temperature to normal levels and 2 to 3 w for a normalization of the biorhythms.

MEITES: I wonder whether many of the effects you have observed would not be the same by simply stressing the animal by one means or another. What sort of hormones have you measured?

OYAMA: We have measured adrenocorticoid steroid levels. My colleague, Dr. Keil, has been involved in some of these studies. After a week or so, or even less, the corticosteroid levels return to normal values. Plasma insulin of rats exposed to 4.1-g go back to prestress levels in about 5 d. The rats show also a pronounced hypoglycemia which lasts for approximately 4 d, and then the blood glucose returns to normal values. At the present time we have work in progress on growth hormones, vasopressin, and angiotensin.

MEITES: You say that the values of corticosterone go up and then they return to normal . . . so the animals adapt.

OYAMA: Yes, the animals adapt, and after they have been in the centrifuge for several weeks you cannot see any difference between the corticosterone levels of the control and the centrifuged animals.

SAMORAJSKI: It might be interesting to take animals at different ages and see what the adaptation difference, if any, would be. It is my guess that the older animals will not adapt so easily.

MIQUEL: We have done, in collaboration with Dr. Oyama, some preliminary work on this problem. Mature mice, 10 to 12 m old, were exposed to 4.1-g for a period of about 4 m. The mature animals lost 4-6 grams of body weight and showed also a high mortality during the first weeks of centrifugation. By contrast, young mice were less affected.

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EFFECTS OF HYPERGRAVITY ON RAT LIVER REGENERATION

David D. Feller

Ames Research Center

I will briefly report on our studies that were begun in preparation for flight experiments. They are related to the growth process and involve regeneration of liver tissue after removing two-thirds of its mass. Liver will regrow to its original mass in a short time, that is, 7 to 8 d; it will not have the same shape, but it will have the same mass. Our proposal was preceded by some experiments on early flights dealing with spermatogenesis and frog egg development. We decided to further investigate the problem of tissue growth by looking at mammalian regeneration. As a way of doing some background work, we followed the regrowth of the liver by measuring the mitotic activity in a hypergravic environment. About two-thirds of the liver mass was removed in three groups of animals. One group was fed ad libitum and left at 1-g; another group was placed on the centrifuge at 2.5-g during the regenerative period following liver excision; and a last group, maintained at 1-g, was pair-fed the same levels of food ingested by the centrifuged animals. In the rats that were centrifuged, no mitotic activity was observed at 20 hr and 24 hr after hepatectomy. Liver regeneration was initiated at 28 hr and continued up to 36 hr before declining. In this experiment it appears that the increased gravity caused a delay in the onset of mitotic activity and a significant decrease in mitotic activity.

We repeated the above experiment with a higher centrifugation g load of 4.7-g, and we compared the data from the 2.5-g experiment with the data of the 4.7-g experiment. With the increased g load at the 28-hr period, there was no appreciable mitotic activity; then, at the 36-hr period there was significant decrease compared to the animals whose liver was regrowing at 2.5-g. With these two data points, one can conclude that the higher g load delays the onset even further, and the magnitude of the mitotic activity at the 36-hr period was significantly lower. The experiment was performed with intact animals that were exposed for 4 wk to a gravity load until they became adapted. They were then removed from the 4.7-g exposure, returned to the laboratory 1-g, operated on, and followed for liver regrowth in the 1-g environment. The centrifuged animals which were brought back to 1-g from 4.7-g did exhibit mitotic activity in their livers at the 24-hr period; at the 28-hr period, the centrifuged animals showed significantly greater amounts of mitotic activity, and at the 36-hr period this increase persisted. If one took the liberty of plotting these curves, it would appear that in the livers of animals that were first adapted to the increased gravity and brought back to 1-g, the onset of regeneration occurred at an earlier time and there was some enhancement.

DISCUSSION

COMFORT: Did you follow any of these experiments to see what the percent of restoration was in the liver when regeneration was completed?

FELLER: Yes, and in every case the total amount of regrown mass of liver was the same.

COMFORT: I was wondering if centrifugation mimics the aging process. In old animals there is a delay in mitosis and the final mass regenerated is somewhat smaller.

FELLER: The only effect of gravity on the regenerative process was at the very early stages up to the first 2 d post surgery and, thereafter, the tissue regenerated to a comparable mass.

KRAFT: If older animals had been used, perhaps the results would have been different.

SHOCK: My recollection is that in terms of total liver mass, regeneration of the old animals did as well as the young. The differences were again in the rate at which they regenerated (Bucher, N. L. R., and Glinos, A. D.: The Effect of Age on Regeneration of Rat Liver. Cancer Res., vol. 10, 1950, pp. 324-332).

COMFORT: I think they did almost as well. The results probably depend on the investigator doing the work. I believe some research has shown a 5% difference in final mass.

MEITES: Am I correct in concluding that liver regeneration decreased when these rats were placed on increased g, but if they were conditioned first, then you actually saw an increase in the ability to regenerate liver tissue?

FELLER: If you place the rats on the centrifuge at increased g, the initiation of mitosis is delayed. For the earlier time periods the amount of mitotic activity is decreased, but if you go beyond those first few days, up to 7 or 8 d, then the total amount of the liver that is regrown is the same. Centrifugation, as far as total final regrowth is concerned, did not show a change. If you adapt the animals to hypergravity and then return them to 1-g, the initiation of the regenerative process occurs sooner. The mitotic activity at the earlier time periods is greater in the animals that have been returned to Earth's gravity, but at 7 or 8 d after hepatectomy the total mass of liver is about the same.

SACHER: You might actually find overshoot in that case, because they are responding to the signal of the higher metabolism associated with the centrifugation.

KLEIN: Can you really say that any of these data is a gravity effect? We heard earlier that in the first day or two the rats exhibit a marked stress reaction when they are put on the centrifuge. Did you stress the animals in any other way than by centrifugation and then look at mitosis?

FELLER: In the metabolic studies with regard to synthetic activity, exposure of the animal to centrifugation at 2-, 3-, or 5-g, no gravity effects were observed. An increase in blood glucose was seen, but it did not correlate with the gravity load. By contrast, in our experiment, the liver regeneration correlated with g.

SPACE WEIGHTLESSNESS AND HORMONAL CHANGES IN HUMAN SUBJECTS AND EXPERIMENTAL ANIMALS

Richard E. Grindeland

Ames Research Center

So far no clear pattern of hormonal changes during spaceflight has emerged. Moreover, the available data are difficult to interpret. Before proceeding to consider hormonal data from manned and animal flights, I would like to briefly discuss the difficulties in interpreting these results. In manned flight experiments the number of subjects is small, typically three per flight, which creates problems in attempting to analyze the data statistically. Secondly, it has already been mentioned that in the Apollo and Kosmos flights the complicating effect of reentry was present. Once the organism is exposed to the high gravitational force of reentry the plasma levels of hormones may be distinctly different from what they are in flight; it is well known that a number of hormones such as ACTH and prolactin are responsive to stress, presumably including reentry stress. A third consideration in interpreting the data is that blood samples of human subjects during flight have been taken at various times and may be affected by biorhythms, irregularity of food intake, and the differing duties and responsibilities of the various crewmembers, all of which can affect plasma hormone concentrations. In the Apollo and the Gemini flights, difficulty was encountered in preserving urine specimens, thereby raising some doubt about that data. Lastly, in the Kosmos flights a rat diet has been used that is unusual by our standards. The Russian diet consisted, as a percent of total calories, of 18% protein, 24% fat, and 57% carbohydrate. The flight diet was in paste form with a water content of about 65%. In contrast the percent of utilizable calories provided by these three foodstuffs in American rodent diets are typically 24-28% for protein, 10-16% for fat, and about 60% for carbohydrate. What, if any, effect the differences between Russian flight diet and stock American rodent diet have on endocrine function is unknown, but one must temper evaluation of Kosmos hormone data with the knowledge that the diets are different.

If one looks at the data from spaceflights and bed-rest studies, there are, nevertheless, certainly suggestions of hormonal changes. A number of metabolic effects of spaceflight, namely increased electrolyte excretion, changes in water balance, and loss of calcium and nitrogen, suggest altered endocrine function. In addition, rats on the Kosmos 782 flight gained about 18 grams less than control animals. Although the difference in growth between flight and control animals was not great, it was statistically valid ($p < 0.05$) and conceivably would have been greater on a less caloric diet. Tibia lengths of flight rats were not shorter than those of controls, but it should be mentioned that the quantity of growth hormone required to produce linear growth of bone is less than that needed for increase in body mass. The red blood cell mass also appears to be decreased in both men and rats. Weights of the thymus gland and the gastrocnemius and soleus muscles were invariably smaller after spaceflight. One of the possible causes for the smaller muscle mass of flight animals is endocrine dysfunction; the decreased thymus weights are very probably the result of an endocrine imbalance. Collectively, metabolic and organ weight data argue for altered endocrine function during spaceflight. Hormones have been measured in plasma samples obtained from astronauts in flight or immediately postflight, bed-rested subjects, and rats recovered from 20 d in space. Urine

samples collected from astronauts in flight and rat pituitary glands have also been assayed for a number of hormones.

At recovery, rats from the Kosmos 782 flight had control concentrations of growth hormone in their pituitary glands but decreased plasma levels of the hormone. The best data on human growth hormone levels are from Skylab astronauts in which plasma concentrations of the hormone were essentially normal through 10 weeks of flight and then fell below preflight titers. Bed-rested subjects showed small but statistically significant decreases in plasma concentrations of the hormone. Prolactin has not been studied in men during either actual or simulated spaceflight (bed rest) but plasma concentrations were decreased in rats at recovery. In view of its newly described role in water and electrolyte regulation, prolactin merits thorough investigation in spaceflight subjects. Data from the Skylab on adrenocorticotropic hormone are uneven and inconclusive. The enlarged adrenals of the Kosmos rats certainly suggest elevated ACTH secretion over a protracted period of flight and not merely a response to reentry. Skylab astronauts had variable but essentially normal plasma cortisol levels in flight, indicating a disparity between human and animal responses; urinary cortisol measurement in the Skylab and Apollo flights suggested elevated cortisol secretion. The reasons for the disparity in cortisol values from plasma or urine measurements are not evident. Elevated TSH and thyroxine have been reported for postflight plasma samples from Skylab astronauts and Russian cosmonauts. However, rat plasma and pituitary concentrations of TSH were similar to those of control rats in the Kosmos 782 experiment. These rats also had control levels of LH and FSH in their pituitaries and plasma. The testes of flight rats (mg/100 g body weight) were about 7% smaller than those of controls; while this difference was not statistically significant, it suggests that flight animals may be secreting less FSH. Urinary aldosterone increased in Skylab astronauts whereas plasma concentrations did not differ from preflight concentrations. Plasma parathormone increased significantly in the last days of the Skylab flight and urinary hormone was higher post than preflight. Insulin concentration in plasma fell after 20-80 d of flight and remained low for the remainder of the flight. Although none of the foregoing suggested that hormonal changes have been rigorously established as a consequence of spaceflight, further critical evaluation of endocrine function in spaceflight is certainly warranted.

DISCUSSION

PHILPOTT: Did you mention that the testes of rats exposed to weightlessness weigh less than the testes of control animals?

GRINDELAND: My recollection is that there was about 100-150 milligrams difference per testis. I think the weight was about 1400 mg in the controls and 1285 mg in the flight animals.

PHILPOTT: With Dr. Alpert from the Berkeley Lawrence Radiation Laboratory, we have seen that there is a loss of weight in the testes of mice exposed to particle radiation from cyclotron sources. Since our electron microscopic study has shown changes in sensitive cells from the testis, I wonder if hits by cosmic particle radiation could play a role in the testis loss of weight in spaceflown rats.

MEITES: It seems to me that the reduction in thymus weight goes along with the increase in adrenal weight and the increase in corticosterone in rats. Prolactin

certainly could be very interesting because, in addition to its possible effects on electrolyte metabolism, it is as much an indicator of the effects of stress as ACTH. We first reported this in 1960, and it has been widely confirmed in humans as well as in animals. Stress, including surgical or even mental stress, can result in an increase in prolactin in the blood.

SAMORAJSKI: Is it possible that the prolactin change is related to hypothalamic action and therefore reflects dopamine alterations?

MEITES: There is a lot of evidence that dopamine has a great deal to do with the regulation of prolactin secretion in rats and, of course, in human subjects. If one gives L-dopa to a normal human subject or to a rat, blood prolactin levels will go down. Another item that fits in the Skylab studies is the decrease in plasma insulin and growth hormone. Growth hormone (GH) is well known to increase insulin secretion; in fact, it is believed to be a major factor in regulating blood sugar levels as shown by Young and even before by Houssay. This is a major mechanism to counteract the effect of insulin on blood sugar levels. Insulin, of course, brings blood sugar down, and growth hormone brings it up. In fact, one can produce experimental diabetes in dogs and cats by injecting growth hormone for long periods of time. This was done a long time ago by Evans and his colleagues in Berkeley. If this relationship between growth hormone and insulin holds true during spaceflight, it is very interesting.

GRINDELAND: If the major physiological stimulus for growth hormone secretion is physical activity and if the astronaut is not working too hard during spaceflight, it is very possible that his growth hormone levels will go down and with it the insulin.

MEITES: In human subjects, both growth hormone and prolactin show marked elevations during deep sleep (RM sleep). There is no evidence that this occurs in rats, although they sleep at different times of the day. There are oscillations in serum GH levels which occur about every 3-4 hr, and the plasma growth hormone levels go from practically nothing up to 200 to 300 nanograms per ml. This presents a problem in measuring GH and other hormones as well. It is very important for anyone who works with rats to collect blood samples at the same time of the day, because there are other variations in addition to these oscillations that occur throughout the day, including effects of food intake, physical activity, and so on. Blood samples have to be collected under very uniform conditions in order to make sure that the hormone measurements are meaningful.

GRINDELAND: This was taken into consideration in the bed-rest studies, although I am not sure that it could possibly be done on spaceflight.

SACHER: My data on the daily activity patterns of individual mice indicate that one animal can have a very different pattern from another. Perhaps to be on the safe side, one should take samples from animals that are at the same stage of activity at the time of sampling, or use some predictor of sleep, rather than to take the samples at the same hour of the day.

KRAFT: Another point is that experimental animals should be conditioned in handling by the same payload specialists who are going to work with them during spaceflight, which would minimize stress reactions. This is an important issue, and here at Ames we are attempting to formulate some recommendations for the kinds of controls that will be necessary for the Shuttle experiments.

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EFFECTS OF WEIGHTLESSNESS ON BONE AND MUSCLE OF RATS

Emily M. Holton

Ames Research Center

As most of you may know, there is really a paucity of data on the effect of weightlessness on animals. The best data we have were gathered on the Soviet Cosmos 782 and 936 flights and are on rats. There are also some data from the Soviets on earlier flights with dogs and a bit of information on a primate and a frog flight from the United States; these animals were heavily instrumented and sorting out stress responses to weightlessness from responses to feeding and other problems that occurred is difficult.

Unfortunately, the Cosmos flights were unattended so that measurements could only be made pre- and postflight, as in the initial manned spaceflights. Thus the amount of in-flight data existing is minimal.

The Cosmos biosatellite is shown in figure 1. A centrifuge to expose flight controls to g forces is located above the block of five cages. In the actual flight each block consisting of five cages has a common food and water source; thus food consumption is measured as the amount consumed by five animals rather than individual rats. Feeding occurs four times a day.

Figure 2 shows the individual cage, which is quite limited in space. A coil located around the cage allows the measurement of gross body movements. Core body temperatures were taken during flight on some rats. Activity and body temperature were the only in-flight data gathered.

The three systems the Soviets have identified as the most perturbed in the rats exposed to weightlessness are the hypothalamic-hypophyseal adrenocortical system, the musculoskeletal system (with which we have been personally involved), and the blood.

The Soviets and the Czechs are extremely interested in whether spaceflight is an acute or chronic stress, and we have collaborated with them in the study of the musculoskeletal system. As could be expected, the muscle most affected by spaceflight is the soleus, which is an antigravity muscle. Only minor effects were seen in other muscles.

We have examined tibias from the last two Cosmos flights and have found some unexpected and interesting reactions. Figure 3 depicts hand-ground cross sections of rat tibial diaphyses. At the periosteum, or outer surface of the diaphyseal bone of the rat, normally bone formation occurs but not bone resorption. On the other hand, resorption occurs at the endosteal surface, which is the surface that lines the medullary cavity. One of the most fascinating observations was an arrest line that extended almost completely around the periosteum of the space-flown rats. Prior to the Cosmos 782 spaceflight, we had never seen such an extensive arrest line in rats of this age. The arrest line in the animals exposed to weightlessness marked the periosteal circumference at the end of the flight. These bone sections were taken from animals killed 25 d after flight; they were in the readapted group. Indications of a similar line were also seen in the flight-control animals, which were

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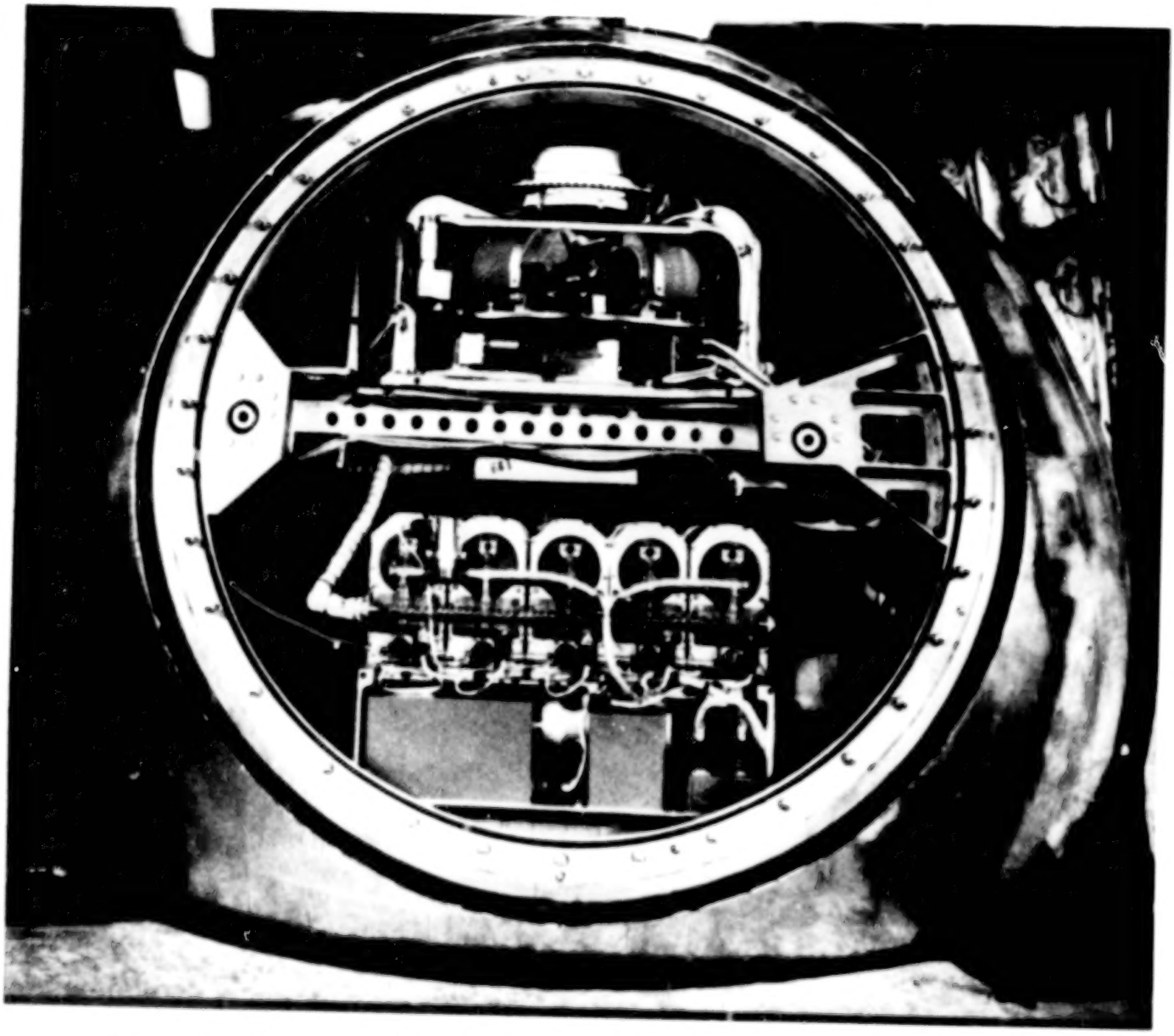

Figure 1.- View of a USSR biosatellite identical to those used in the Cosmos flight experiments.

centrifuged onboard the Cosmos biosatellite; this was also true in the vivarium rats, which were maintained under laboratory conditions of 1-g at all times.

In the bone literature, Frost has discussed an "arrest line," which he thought was a mineralization defect. In our opinion, the arrest line is probably either a matrix defect or a combination of the two; it cannot be due to mineralization alone since we do not see any difference in osteoid width. When there is a mineralization defect, osteoid is laid down but not mineralized.

To measure bone formation rate, we used a tetracyclin derivative, a substance that binds to calcium and is entrapped in bone as it mineralizes. This is a standard technique for measuring bone growth.

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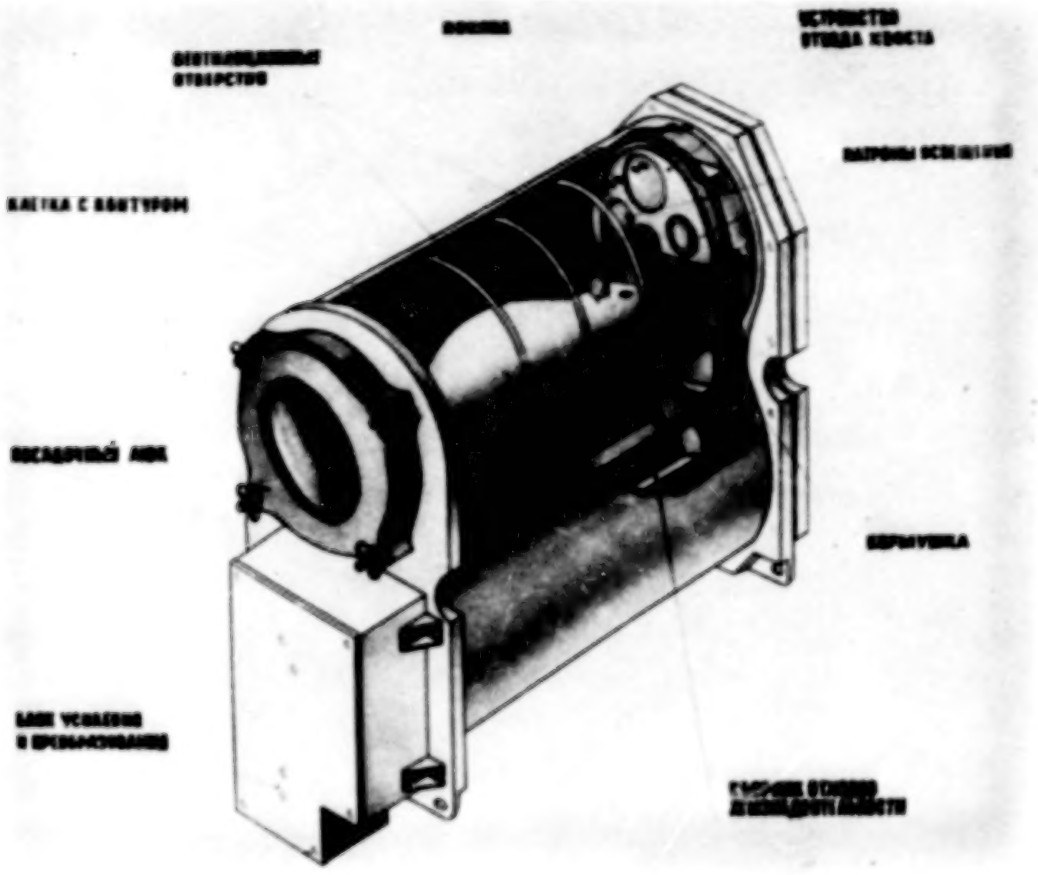

Figure 2.- Drawing of a rat cage of the type used in the Cosmos experiments.

In the experiments illustrated by figure 4, the first tetracyclin label was given 3 d after flight, so the elapsed time between experiments 1 and 2 was 26 d. The time between 2 and 3 is the postflight period, that is, a 23-d period. The figure shows that less bone is formed during flight than postflight at this sampling site, but the data show that, in comparison with control animals, the amount of bone formed during flight decreases about 50%. We saw no gross changes in resorption corresponding to the changes in formation. Resorption was measured by determining the medullary cavity area. Our findings in the tibia of the rats exposed to space weightlessness are somewhat similar to those characteristic of disuse osteoporosis, in which both formation and resorption tend to decrease, but a larger decrease occurs in formation than in resorption. If in addition, zero-g induces a cessation in bone formation, then we might use spaceflight to find out what stimulates the bone-forming cells or osteoblasts.

As I said before, the third system in which the USSR biologists are interested is the haematological system because of the finding of decreased red blood cell mass in rats exposed to zero-g. This is a problem that has been investigated by Dr. Henry Leon here at Ames Research Center.

Other subtle changes produced by weightlessness have been reported by the USSR biologists in some recent articles published in the Journal of Aviation, Space and Environmental Medicine.

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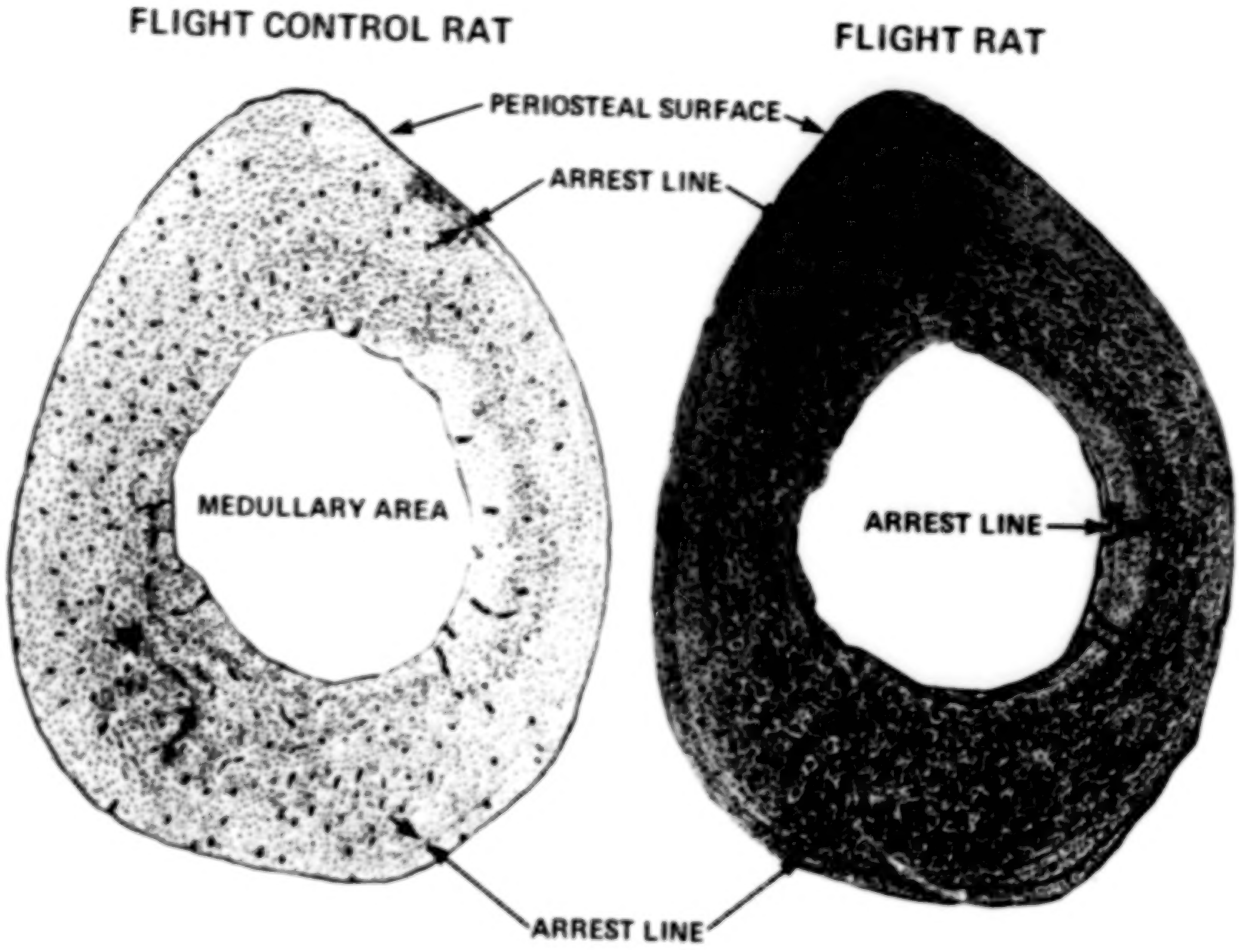

Figure 3.- Cross section of rat tibial diaphyses of a control and a space-flown rat.

Next, I would like to discuss very briefly the model system developed in my laboratory to simulate weightlessness in rodents. It appears promising and is a totally different approach to that used by most people, who have relied on space restriction or total body immobilization, both of which are very traumatic to the animals.

To produce disuse osteoporosis, the skeletal system has to be unloaded. This has been attempted by either casting a limb or the whole body or by performing nerve section. A serious drawback of those techniques is that rats are quite proficient at eating their way out of plaster casts, particularly if you put them on just one leg, and nerve section requires surgical intervention. Our system, illustrated in figure 5, is very simple and does not induce much stress. It is a quick-connect system with a food dish that snaps in and out to weigh the food. The water bottle is gravity-fed and can be marked for water consumption; it is on a peg and can be moved anywhere on the plastic grid. The animal is bonded with silicon to a harness of Excellite, an orthopedic casting material that is very flexible when warm. With this system the animal is free to groom, can bend and sleep on his head and is free to move around in a 360° arc. The back limbs are unloaded and the rat is positioned in a head-down tilt to cause a fluid shift. We have some interesting data, which we have compared with the Cosmos results, on the effects of restriction in this harness

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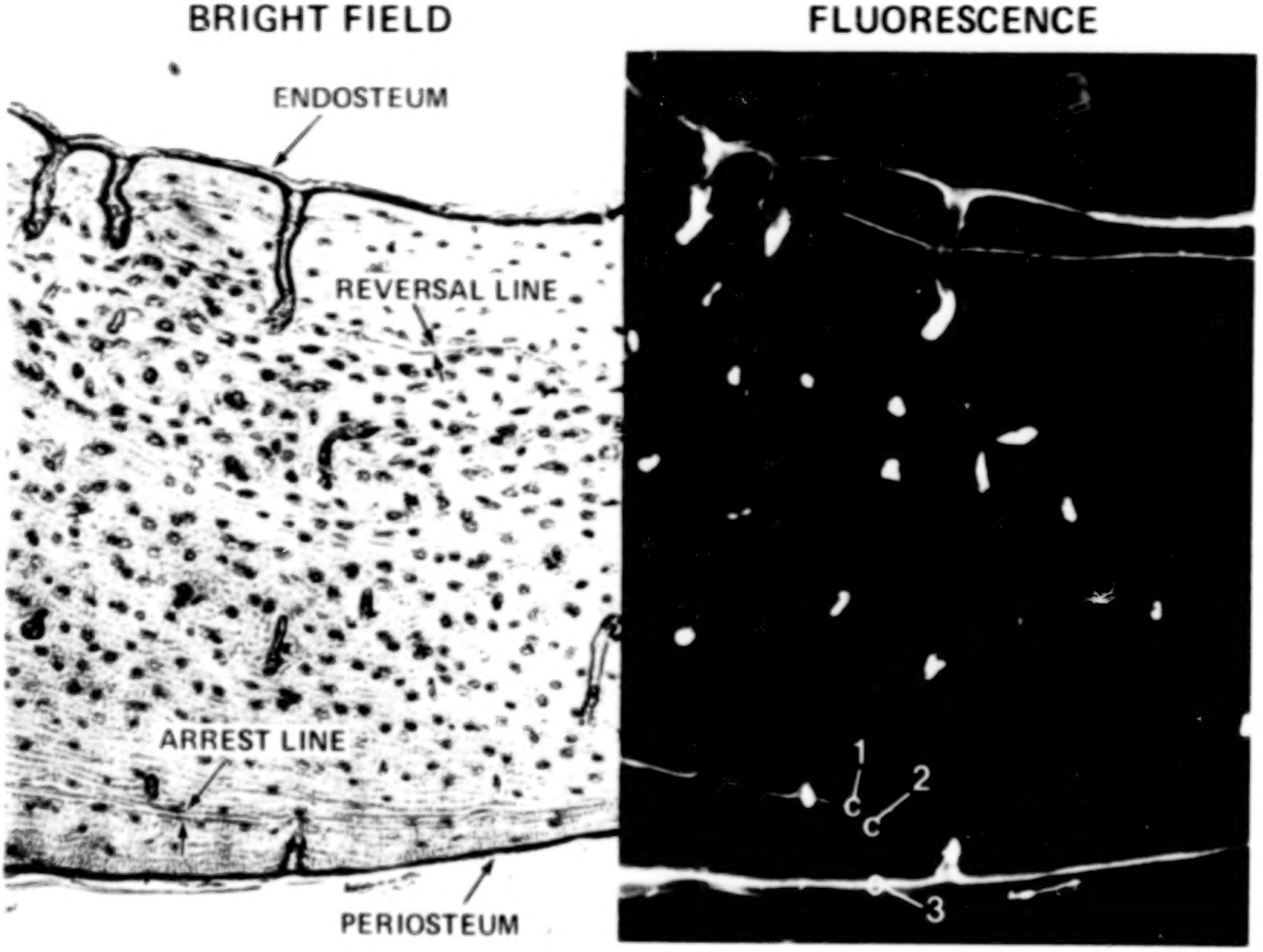

Figure 4.- Cross section of tibial diaphysis of a rat that was exposed to weightlessness for 20 d. The tetracyclin label, which is shown under fluorescent light (right photograph) was administered to the animal at 3 d after landing.

on the leg bone and food consumption (table 1). The Cosmos rats gained about 35 grams per animal during their 20-day spaceflight, in contrast to the controls, whose body weight increased approximately 90 grams on the same amount of food. In our model, the restrained rats gained about 40 grams and the controls, who consumed approximately the same amount of food, gained roughly 20% more weight than the restrained animals.

Summing up, we believe that our harness technique can help to clarify the metabolic effects of hypogravity as related to muscle disuse atrophy and bone decalcification. We have set up a "rat consortium" in collaboration with four scientists from various universities, and our multidisciplinary study suggests that at least some of the effects of harness suspension mimic quite closely the effects of space weightlessness.

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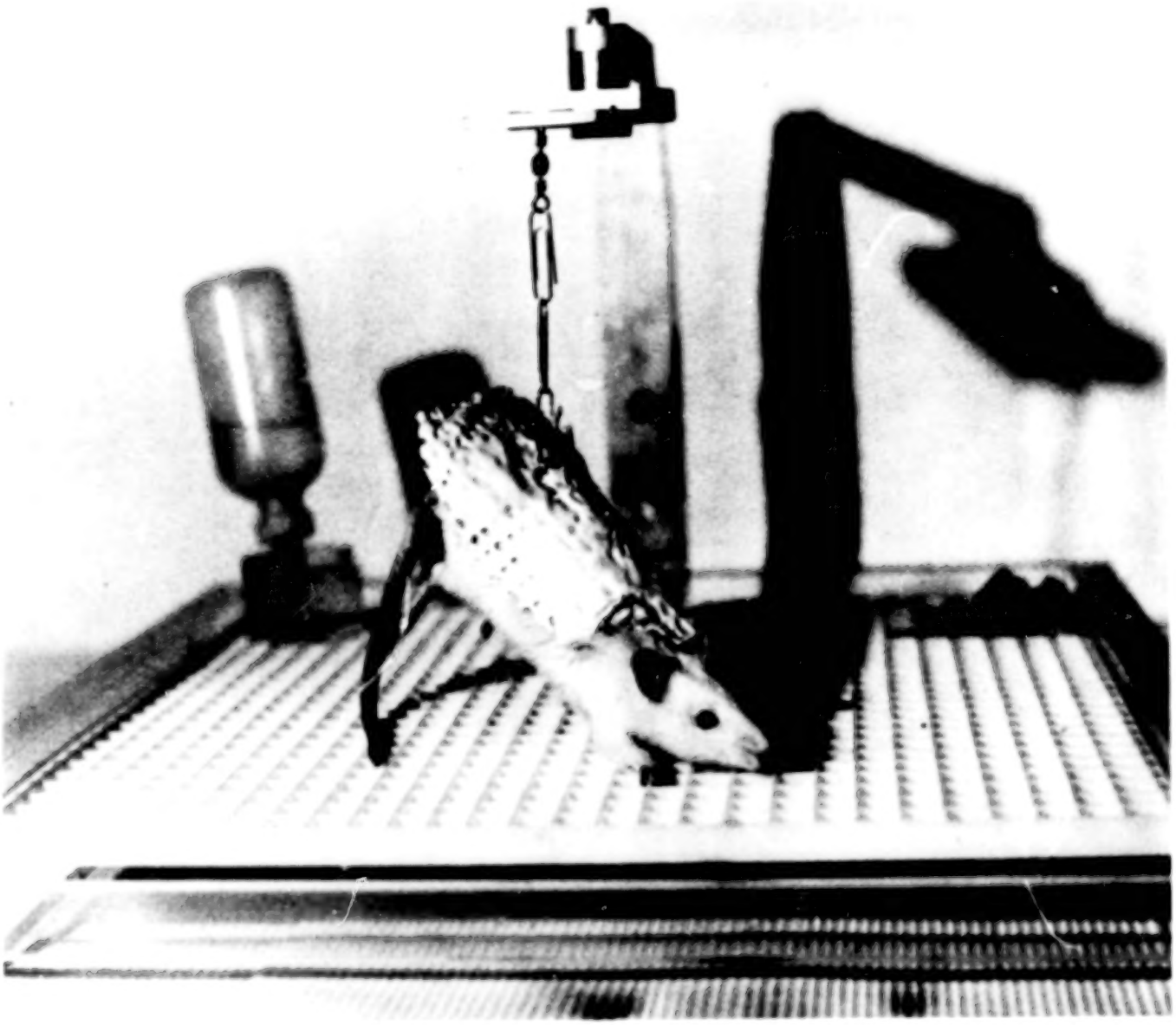


Figure 5.- Technique used in the Ames Research Center studies for laboratory simulation of the effects of hypogravity on leg bone and muscle.

TABLE I.- COSMOS AND RAT MODEL
BODY WEIGHT AND FOOD CONSUMPTION

Group	N	Experimental period, days	Initial body weight, gm	Rate of weight gain, g/day	Rate of food consumption, g/day
Model	9	20	205 ±11.1	1.7 ±0.8	18.3
Pair-fed	9	20	208 ±10.8	3.6 ±0.6	18.3
Weight-matched	10	20	208 ±10.7	1.8 ±0.6	14.5
Cosmos 782	11	23	225 ±8.8	1.5 ±0.6	14.3
Pair-fed	7	23	186 ±12.0	3.8 ±0.4	14.4
Cosmos 936	10	22	212 ±5.1	3.3 ±0.6	18.8
Pair-fed	10	26	194 ±9.6	3.7 ±0.6	16.4

DISCUSSION

SAMORAJSKI: Have you ever considered reversing your model to put the head up?

HOLTON: I am sure that this could be done very easily. Whether it is head up or down depends only upon where you put the paper clip. The animals seem to adapt to this system quite readily. They lose weight for about 2-3 d and then start gaining it back, which contrasts with the data obtained on space-restricted animals. In effect, when rats are restricted in a small cage they do not regain their original body weight for periods of up to 9 m.

In our model the weight recovery seems to be somewhat age-dependent. The older the animal, the longer it takes. We used some animals weighing 250 grams and they required at least 1 wk to adapt. On the other hand, rats just past weaning adapted within 3 to 5 d.

ECONOMOS: Have you looked at the fluid balance in those animals during the first week?

HOLTON: We still have not done this. However, some studies on water balance are presently being done by Dr. Joseph Musacchia in Missouri. He is looking at water loss.

COMFORT: Why don't the effects on bone and muscle show on bed-rested subjects?

HOLTON: This is related to the age of the subjects. There have been some studies showing that if you take young active adolescents and put them in bed, under traction, they develop osteoporosis and can go into hypercalcemic crisis. So you have to be very careful with young people.

MEITES: You mentioned that the USSR biologists have been studying hypothalamic-pituitary-adrenal function. What were their findings?

HOLTON: The main finding that I recall offhand was an increase in corticosterone, but this was seen after a traumatic reentry. In our own studies we have found that simply weighing the animals prior to sacrifice is sufficient stress and that the steroid levels are raised by that. I do not know how you can interpret this, but the Soviet biologists also saw an increase in adrenal weight, after landing, of about 25%.

KRAFT: There were also histological changes such as increased numbers of necrotic cells in the lymph nodes.

HOLTON: Yes, I think that because weightlessness is a new environment for the rats, it takes some time until the animals get used to it. There are all kinds of physiological reactions until the animals learn to operate in space. Of course, this would not happen if the animals were born in space.

The above seems to be true for astronauts as well. In effect, when they engaged in extravehicular activities they found it was much more fatiguing than they had anticipated. There was a tremendous heat output probably due to the effort of holding onto things; they just could not afford to relax.

Another problem particularly felt in Skylab flights occurred when the astronauts went into a room where there were no up or down cues; they found they could become somewhat disoriented.

COMFORT: The emotional effects of spaceflight may be important not just in astronauts but in rats as well. I believe that we should keep this in mind when we try to interpret the effects of zero-g.

HOLTON: The animal experimentation should really be much better in the Shuttle, because we are going to exert much better control. Thus, it will be possible to sacrifice animals before landing so that we can prevent the readaptation phase that starts immediately after reentry.

SACHER: You mentioned a consortium working on this model. What kind of research is being done?

HOLTON: Some people are interested in metabolic aspects. One group is working in the cardiovascular area and another on kidney and guts. Some investigators here at Ames look at as many systems as they possibly can, and then we try to correlate the effects. The collaborators from outside NASA are Dr. Neuszki in Missouri, who is now moving to Louisville, Dr. Popovic in Atlanta, and Dr. Pitts in Charlottesville, VA.

MIQUEL: What has been the longest time of exposure to the harness restriction?

HOLTON: We have exposed rats for up to 21 d, and see psychological reactions in the suspended rats. For the first 2 or 3 d they try to keep their hind feet on the ground all the time. Then, when they seem to realize that this is not possible, they pull their hind legs up and tilt their heads. This, apparently, makes them more comfortable.

KLEIN: Returning to the Cosmos rats, the USSR biologists went through rather extensive behavioral tests in the animals after spaceflight. They put them through mazes and so forth and the conclusion was that spaceflight did not seem to affect any of their learned capabilities.

HOLTON: One other thing the USSR biologists found, that we also see in our harness experiments, is that the animals have difficulty in stabilizing their posture. Thus, we have observed that the rats spread their paws and cannot keep their balance when they come off the harness. The USSR scientists have used posts to check postural control, and they have seen that rats cannot hold onto the posts right after coming back from spaceflight. However, they quickly readapt to 1-g, and then their performance on the poles improves.

SACHER: You called this the head-down position. Do you really attach any significance to the head-down position? Hydrostatically there is only about 1 millimeter of mercury.

HOLTON: The main reason for "head-down" is that you cannot only get a fluid shift, but you slide the organs forward and unload the rear limbs. Organs free-float and push on the abdominal cavity in a way similar to what happens to astronauts in spaceflight, who often complain about a feeling of fullness because their gastrointestinal organs are free-floating in the absence of gravity.

In bed-rest studies, the Soviets have also found that a 4° head-down tilt is a better simulator than simply lying horizontally in bed.

EFFECT OF EXERCISE ON THE PSEUDODIABETES OF BED REST

John E. Greenleaf

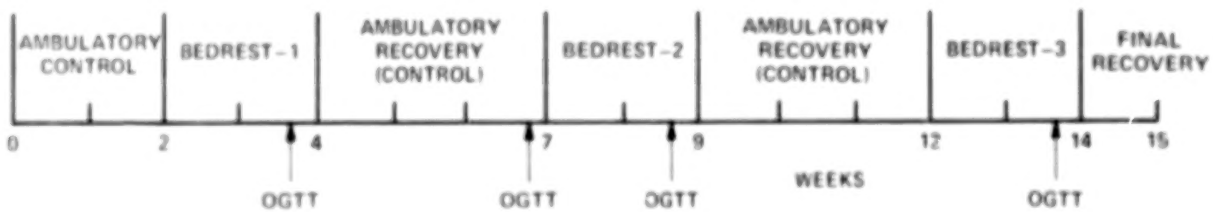
Ames Research Center

SUMMARY

Normal subjects exhibit prolonged hyperinsulinemia and hyperglycemia when given a standard glucose tolerance test after 3 days of enforced bed rest without supplemental physical exercise (refs. 1-4). Daily isotonic exercise during bed rest reduces, but does not eliminate, the degree of "impaired" glucose utilization (refs. 1, 2). This disturbance in carbohydrate metabolism disappears in about two weeks after bed rest with normal, ambulatory recovery (ref. 3), but glucose tolerance returns to normal in less than one week when prescribed physical exercises are employed during recovery (ref. 5). It appears that bed-rest-induced glucose intolerance is diminished with increasing energy expenditure during both bed rest and recovery. We investigated the effect of intensive isotonic exercise and isometric exercise (with its low metabolic rate) during bed rest on plasma insulin and glucose responses to a standard glucose tolerance test. The subjects were seven healthy men, 19 to 22 years in age, 166 to 188 cm in height, and 62.40 to 103.80 kg in weight; maximal oxygen uptakes ranged from 3.36 to 4.38 liters/min.

PROCEDURES AND METHODS

The experimental design and sequence of exercise regimens are given in figure 1. The men remained in the horizontal position throughout bed rest, even when bathing and during excretory functions, but they were allowed to rise on one elbow to eat.



SUBJECT	BEDREST-1	BEDREST-2	BEDREST-3
A	NO EXERCISE	ISOMETRIC	ISOTONIC
B	ISOMETRIC	ISOTONIC	NO EXERCISE
C	ISOMETRIC	ISOTONIC	NO EXERCISE
D	ISOTONIC	NO EXERCISE	ISOMETRIC
E	ISOTONIC	NO EXERCISE	ISOMETRIC
F	ISOTONIC	NO EXERCISE	ISOMETRIC
G	NO EXERCISE	ISOMETRIC	ISOTONIC

Figure 1.- Experimental protocol with sequence of bed-rest exercise regimens; OGTT is oral glucose tolerance test.

Their diet consisted of 14 different daily menus containing 3,073 ±SD 155 kcal/day; it comprised 121 g (20%) protein, 344 g (56%) carbohydrate, and 144 g (24%) fat by weight, 3.8 ±SD 1.0 g Na^+, and 1.6 ±0.2 g Ca^{2+} per day. Water was available ad libitum, but each man was required to drink 225 ml of coffee, tea, or milk, or any combination thereof, with each meal. The diet was started 10 days before each bed-rest period.

The subjects exercised for 1 hr/day at 50% of their maximal oxygen uptakes (565 kcal/day) during the ambulatory-control periods (fig. 1). They also performed isotonic (780 kcal/hr) and isometric (250 kcal/hr) exercises for 1 hr/day during two of the three bed-rest periods. No exercise (90 kcal/hr) was performed during the remaining bed-rest period.

The oral glucose tolerance test (OGTT) was administered on day 10 of each bed-rest period, and the ambulatory-control test was performed on day 21 of the first ambulatory-recovery period (fig. 1). The dose of glucose administered was 40 g/m^2 of body surface area (ref. 6); the average dose was 82 g (range, 68-94 g). Plasma glucose was measured with the glucose oxidase method, insulin by radioimmunoassay, and plasma volume with Evans blue dye. Results were analyzed with the t-test for dependent data, and the null hypothesis was rejected when $P < 0.05$.

RESULTS AND DISCUSSION

Anthropometric Responses

In the ambulatory-control periods, mean basal body weight decreased between 2.1 and 2.4 kg ($P < 0.05$) during dietary equilibrium and remained essentially constant during bed rest with no exercise (-0.4 kg, NS), but declined by 0.9 kg ($P < 0.05$) with isometric exercise and by 1.8 kg ($P < 0.05$) during bed rest with isotonic exercise, due in part to the increased energy expenditure of about 780 kcal. About one-third of the weight reduction with isotonic exercise was due to fat loss (0.7 kg), and the remainder (1.0 kg) to loss of lean body mass (ref. 7). The loss of lean body mass was caused by assumption of the horizontal body position, and the loss was independent of the metabolic rate. The reduction of body fat was directly proportional to metabolic rate.

Basal Plasma Volume and Glucose

In the three control periods, basal plasma glucose concentrations were within the normal range (83-84 mg/100 ml) (fig. 2). Compared with their respective pre-bed-rest control values, basal plasma glucose concentrations increased ($P < 0.05$) during the two exercise regimens by the second day of bed rest, probably reflecting the reduction in plasma volume (hypovolemia) (ref. 8). At the end of bed rest, the glucose concentrations had returned to control levels, but there were increases to the above control levels, particularly following the no-exercise regimen, on the third day of recovery. Plasma glucose contents fell progressively during bed rest and, by the end of bed rest, they were lower in all subjects (no exercise, 434 mg, -15%; isometric, 365 mg, -12%; and isotonic, 304 mg, -11%) than respective control values (fig. 2).

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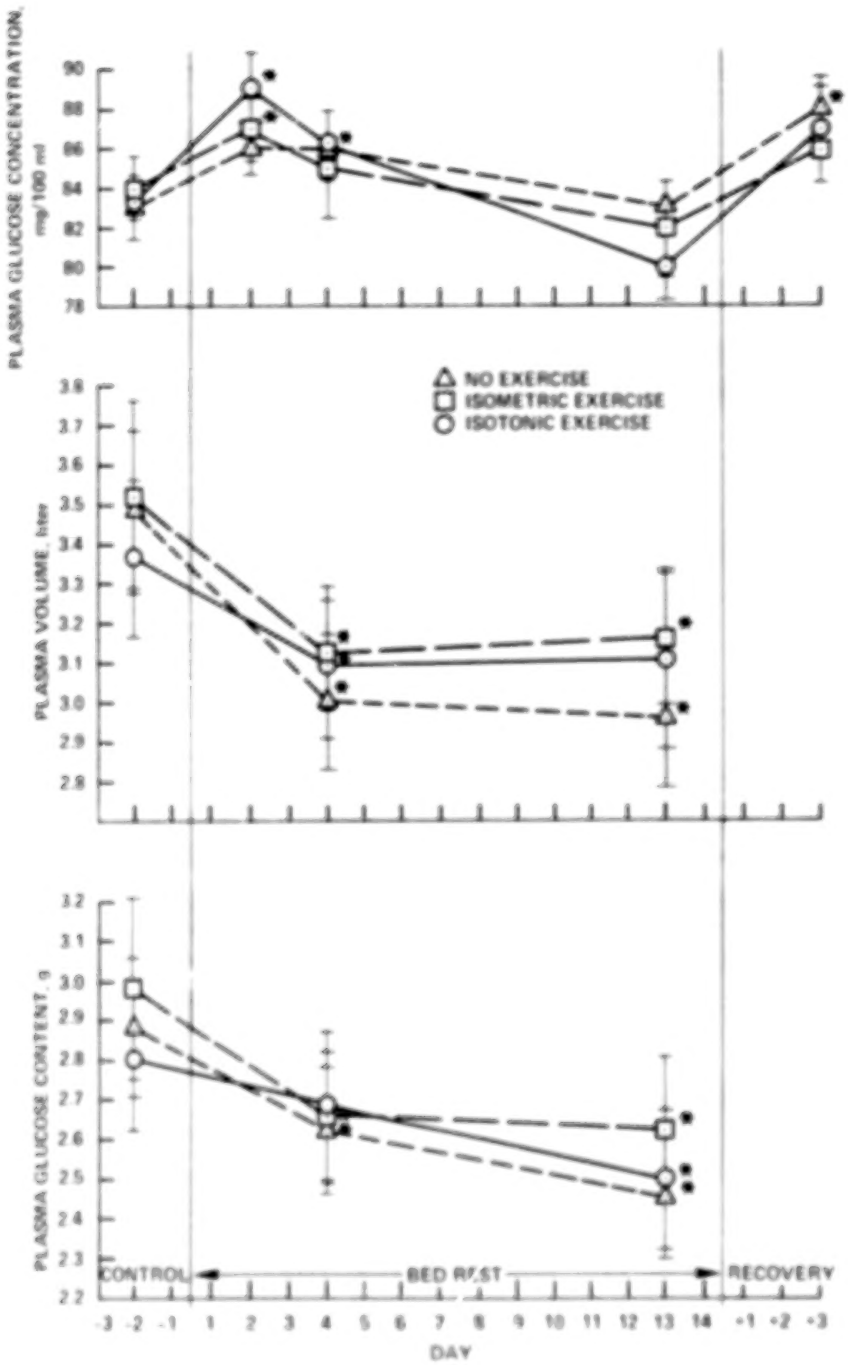

Figure 2.- Mean (± SE) plasma glucose concentrations, plasma volume, and glucose content changes during ambulatory control, bed rest, and ambulatory recovery periods for the three exercise regimens; *P < 0.05 from day minus 2.

Responses to Glucose Tolerance Test

The integrated areas under the insulin and glucose response curves during the 3-hr glucose tolerance test are presented in figure 3. The areas under the glucose curves were less variable than the insulin responses, but there was a similar trend of decreasing response with increasing metabolism. The greatest insulin response occurred with the no-exercise regimen, followed by progressively attenuated responses

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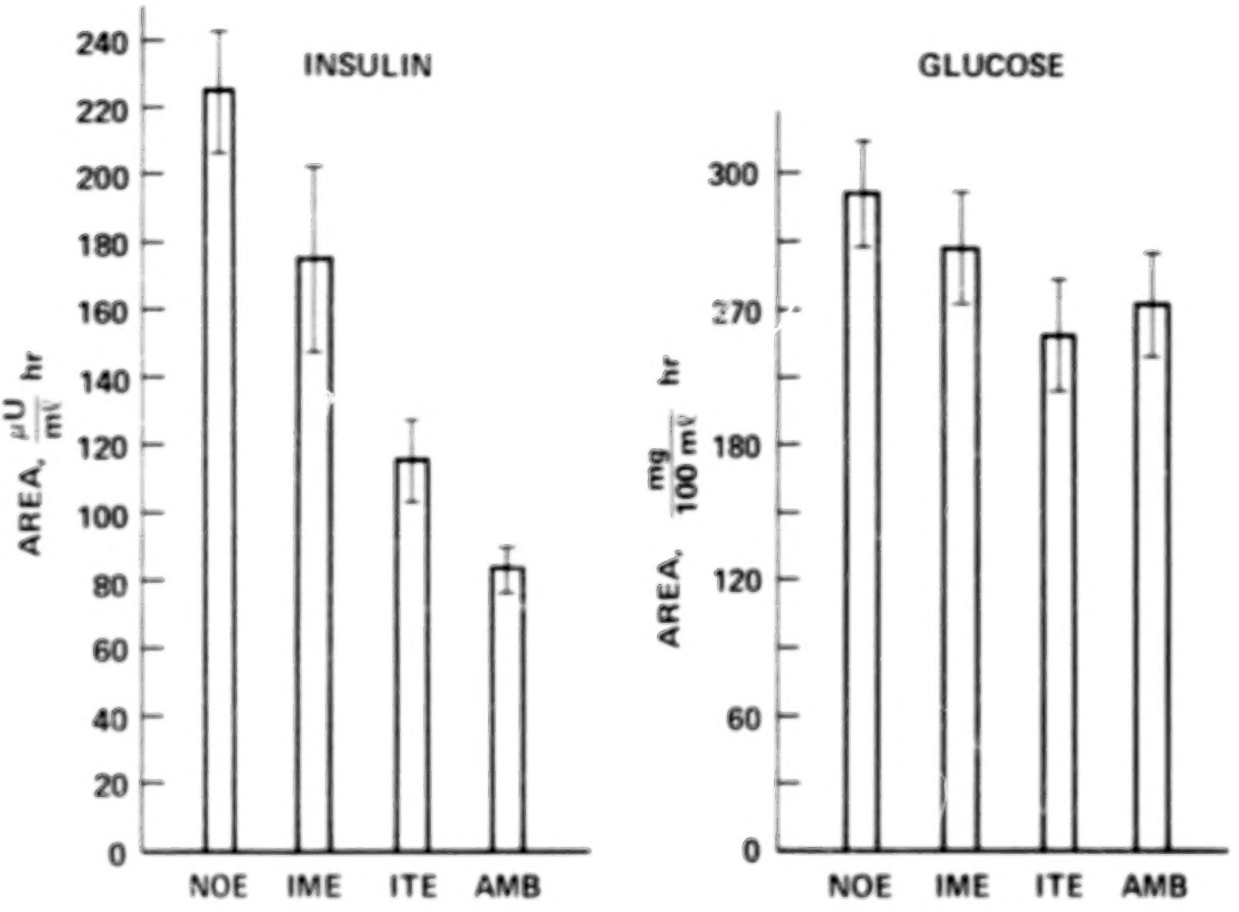

Figure 3.- Mean (± SE) integrated areas under the insulin and glucose curves during the 3-hr glucose tolerance test for ambulatory-control (AMB), no-exercise (NOE), isometric-exercise (IME), and isotonic-exercise (ITE) regimens.

with isometric exercise, isotonic exercise, and ambulatory control. The decreasing insulin responses were proportional to increasing total energy expenditure and the relationship was linear (fig. 4). The linear regression of the insulin area on the total daily energy output (rest plus exercise) for the three bed-rest regimens indicates that an energy expenditure of about 3,000 kcal/day is needed to normalize the insulin response. If 90 kcal/hr are utilized for 22 hr during bed rest (1,980 kcal), then about 1,020 kcal/2 hr must be obtained from supplemental exercise. This additional energy expenditure could be met by 1 hr/day of each of the isotonic (780 kcal/hr) and isometric (250 kcal/hr) exercise regimens used in the present study. It is not certain that elimination of the hyperinsulinemia would restore the glucose responses to normal. Clinical findings indicate that the longer the period of inactivity during bed rest, the greater the frequency and amplitude of abnormal glucose tolerance curves (refs. 1, 9).

These results suggest that some factor, perhaps related to the gravitational vector but inversely proportional to total daily energy expenditure, is involved in the mechanism of this "abnormal" carbohydrate metabolism during prolonged bed rest.

The "inappropriate" response of the elevated glucose concentrations during the tolerance test to the large insulin concentrations suggests that (1) insulin activity is changed by, perhaps, the release of an insulin inhibitor; (2) there may be blockage of the function of a second factor with insulin-like activity; (3) some aspect of

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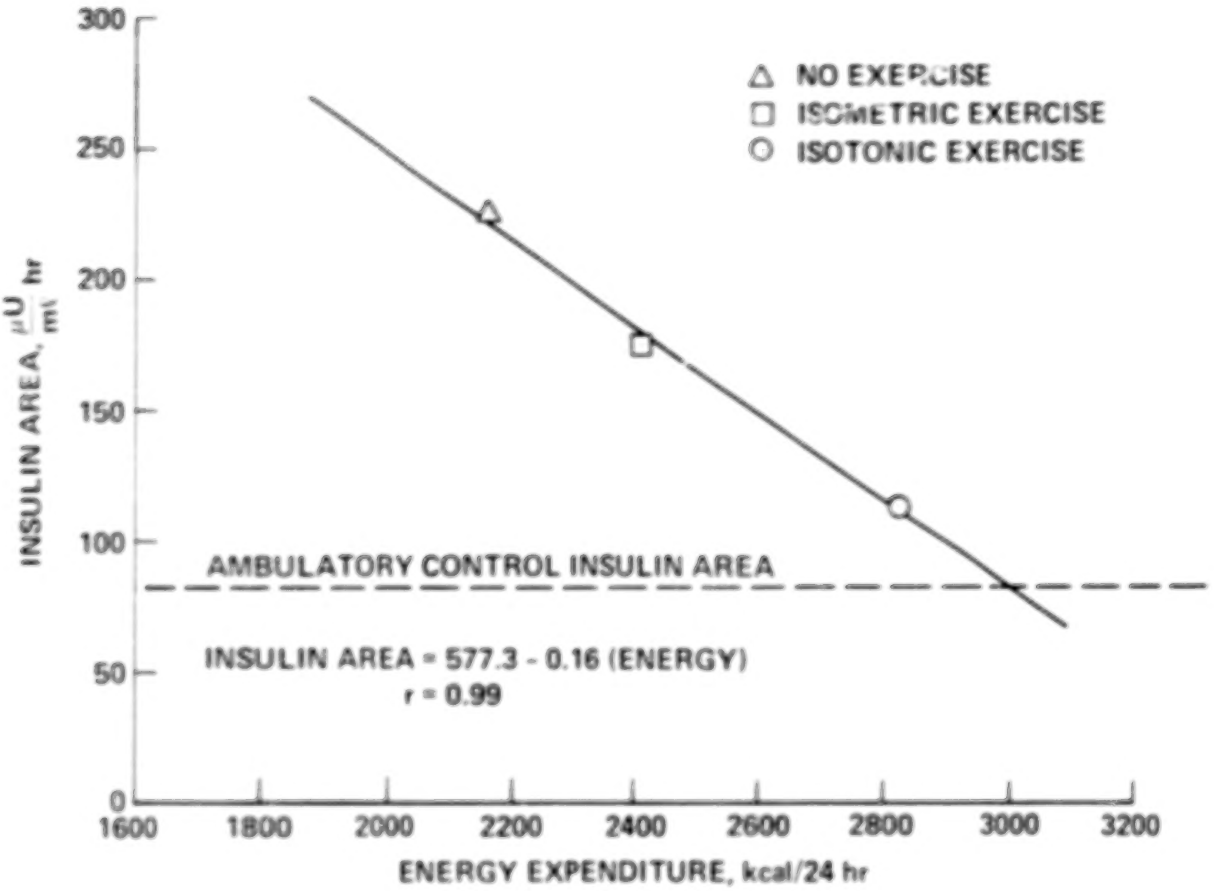

Figure 4.- Regression of the integrated areas under the insulin response curves during glucose tolerance tests on the 24-hr energy expenditures for the three bed-rest regimens.

cellular membrane function is changed; or (4) perhaps some combination of the above. The evidence indicates insulin synthesis and release mechanisms are functioning normally (ref. 10). The problem appears to reside in or about the cellular membrane, and some factor or factors activated by physical exercise that respond to the quantity of energy expended are necessary for insulin and probably glucose to respond normally. Men undergoing intensive physical training have a more efficient glucose metabolism with very little increase in plasma insulin concentration; that is, a greater insulin sensitivity during a resting glucose tolerance test compared with that of normal, untrained men (refs. 11, 12). Baile et al. (ref. 13) have hypothesized that increased blood lactate with exercise induces the release of a factor that increases the rate of glucose metabolism. Lactate itself might alter the function of the cell membrane to promote increased influx of glucose (ref. 14).

From a clinical perspective, it seems that high-intensity, intermittent, isometric leg exercise provides some remedial effect, but the most efficient and practical method of increasing energy production is with isotonic exercise that utilizes the large muscle groups of the legs.

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LIFE SCIENCES EXPERIMENTS ON THE SPACE SHUTTLE

Richard D. Johnson

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We are now in the process of putting together a plan to perform a variety of Life Sciences experiments in a space laboratory. The Shuttle (figs. 1 and 2) is designed as a space truck; it does not have the ability to stay in space for very long periods of time. The Shuttle will have crews of five to seven, including a pilot and copilot. It is configured very much like a plane, and the g levels are quite reasonable, not exceeding 2.5- or 3-g's during takeoff or landing. The engineering aspects of the program are presently being developed, and the first actual missions have been scheduled for the 1980s. The first are a series of flights,

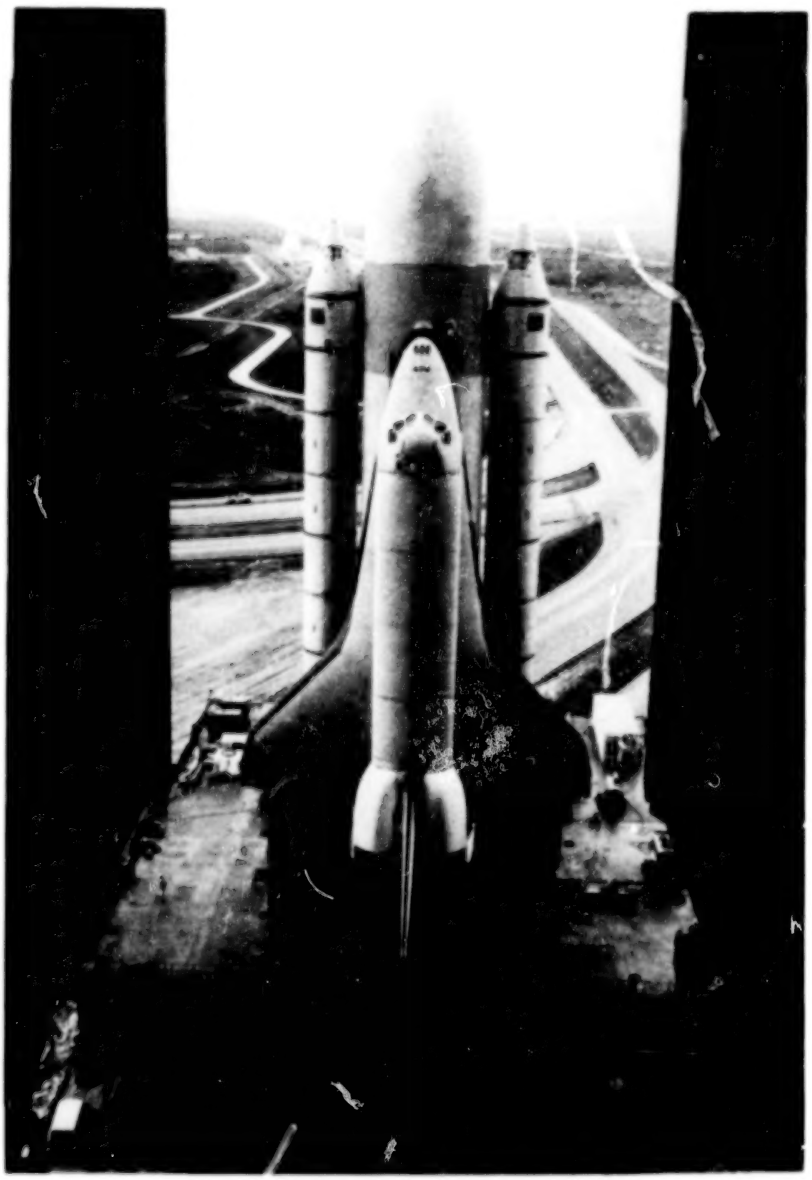

Figure 1.- The Shuttle standing in its launching pad.

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Figure 2.- Side view of the Shuttle.

called OFT, which are test flights but will also be used to perform some scientific experiments. Following these missions, the first Spacelab is expected to fly in 1982. This will be a joint mission with European scientists. The experiments have already been selected, but there is still a lot of the system to be worked out. The second Spacelab mission will be a pallet-only mission with no laboratory facilities available. The few Life Sciences experiments selected will be flown in the crew cabin. Starting with Spacelab No. 3, the participating scientists will be able to have their experiments in a laboratory environment where standard procedures can be used (see fig. 3). We hope we will be able to make experimentation for the space investigations as simple as possible. Currently, we are planning on testing our animal-holding facilities on this flight. Some subsequent flights will be entirely dedicated to Life Sciences.

The first missions will only be seven to ten days in duration. After several years, the duration of the flights may increase to three weeks. This is because of limitations in power, oxygen, and other consumables. Thus, what we are going to see in the 1980s is the growing opportunity of doing good experiments of very limited duration. Beyond 3-4 wk, we will need a vehicle that can be left behind in space like Skylab.

There are two possible ways of doing flight experiments — one is by filling the whole Spacelab with Life Sciences experiments (called dedicated labs); the other is by subdividing the available laboratory space and having three or four racks for the

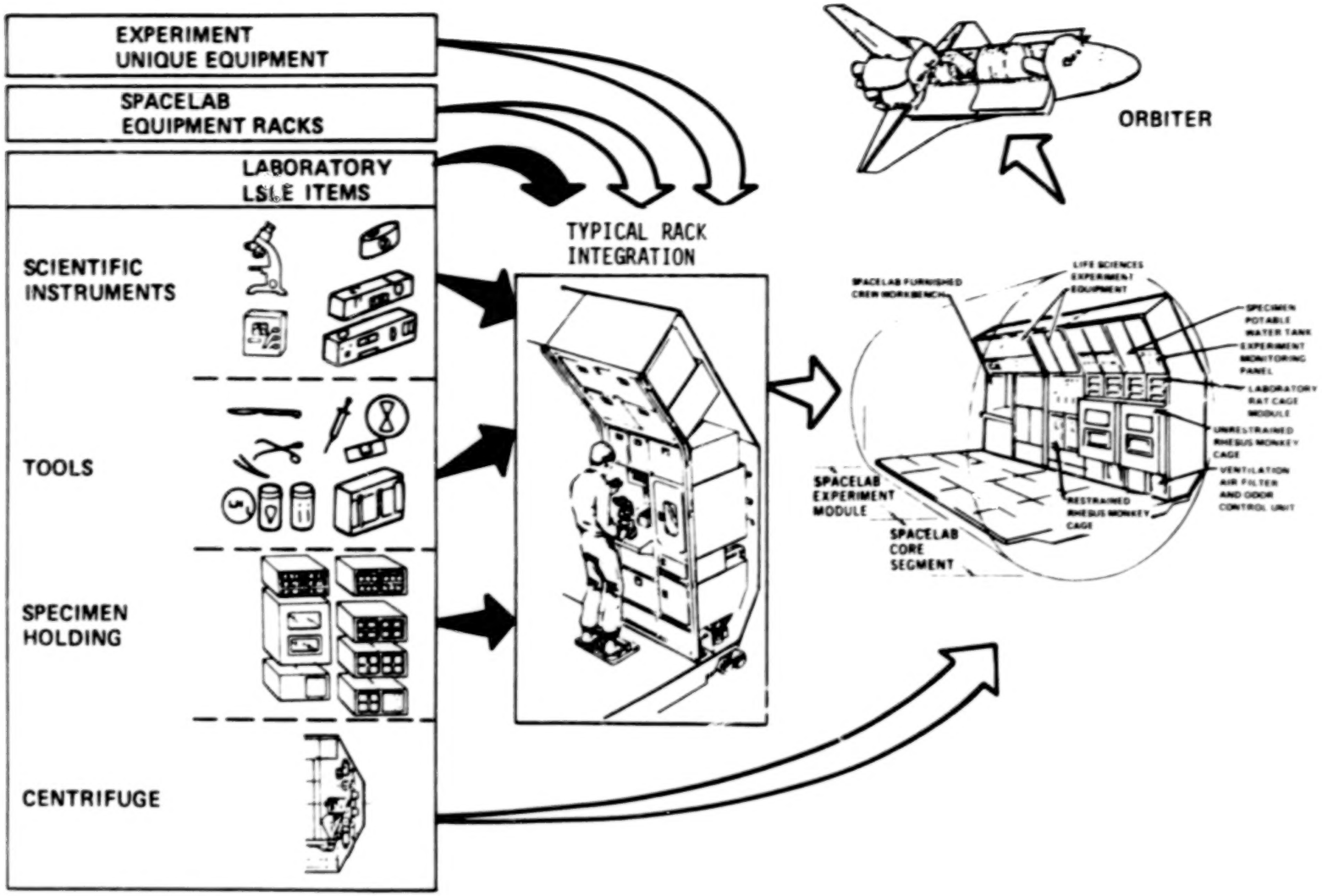

Figure 3.- Life Sciences payload experiment development.

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biological experiments and using the remaining space for scientists who study processing of materials in space or who have consoles and screens for telescopes, and so forth. This is the minilab concept.

For experiments dealing with biological and biomedical problems, our main effort has been the development of the equipment and the procedures needed to work with animals in space. Examples are taking blood samples from experimental animals, demonstrating the effects of certain drugs, performing metabolic studies, etc. Our focus has been on equipment needed as standard items for a space laboratory so that scientists can use them again and again. An example is a microscope that may be an essential piece of equipment for many experiments. Others are kits for blood and urine collection and analysis. We are also developing systems to hold animals, especially rats and monkeys (fig. 3). These cages provide for the feeding and watering of the animals in weightlessness. They also include the equipment needed to provide the animals with a clean and conditioned atmosphere. The wastes are blown down through a coarse grill in the floor onto a screen and held there for evaporative drying. The urea and ammonia are trapped on a chemical and charcoal bed for control of odors. The noise levels may be very high during takeoff, reaching 135 decibels for about one minute. The spectral characteristic is mostly 400 to 1000 hertz. This could be traumatic, but initial tests have shown that we do not have to provide sound insulation for the animal cages. The Shuttle lands like an airplane. It is important to unload the experiments soon after landing and to use animal transporters to speed the unloading so that specimens will not be compromised.

The cages have controllable lighting and air flow. They also have activity monitors. It is doubtful that the animals will be taken out of their cages into the open Spacelab during actual spaceflight, owing to a variety of safety and hygienic considerations. Instead, we will use an enclosed workbench for animal surgery and miscellaneous techniques. It has air flow like a fume hood, with a door in the front which has access holes for hands. The whole unit is mounted on hinges that allow access from both front and back. We will also have on board Spacelab a number of packaged kits with the supplies needed to perform specific jobs. Everything will be kept in its place, and after use things will be stored or disposed of. There will be several balances to weigh samples ranging in weight from 1 mg to 1 kg and storage spaces to take care of the waste management problem. Also included will be freezers and refrigerators for storing specimens. The workbench can accommodate other equipment. For example, we tested a procedure to take movies of the activity and mating behavior of insects exposed to weightlessness. The camera was fixed in certain locations in the bench with lights and subsequently disassembled and stored in drawers after the experimental session.

Surgical procedures can also be performed on board the Spacelab in the workbench by properly trained personnel. One worry is how to handle fluids in a weightless environment. We propose to use plastic containers and plastic bags, which are very handy for mixing fluids.

The general principle in our planning is to do in space only the procedures that cannot be delayed until coming back to Earth. Thus, if blood samples or animal tissues can be safely preserved by freezing or histological fixation, we will store them on board until the end of the mission after which they can be investigated in ground-based facilities.

More sophisticated equipment has been studied for use in experiments involving primates. The animals might have to be restrained; gaseous total metabolism might be measured. Some investigators even wish to utilize stereotoxic electrodes in the

brain. Implantation of catheters and instrumentation can result in problems where it is sometimes better not to be so ambitious. Recording of EEGs and blood flow are possible, but the animals will not be so heavily instrumented as in some previous flight experiments.

One last point is that even though the Shuttle program has been curtailed by budgetary cuts, we will still be able to do adequate experiments — perhaps not every six months as originally planned, but often enough to accommodate a whole series of experiments on plants and animals up to and including squirrel monkeys. Eventually, larger animals, more complex experiments, and longer-duration missions will be possible.

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ENERGY METABOLISM AND LIFESPAN

George Sacher*

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I shall discuss some aspects of the relation of energy metabolism to longevity. This is a problem that has intrigued me for many years. The background was that I compiled a good set of data on the species lifespan and the adult resting or standard metabolic rate (in units of calories per gram hour) for 85 mammalian species and found a negative allometric relationship between these two variables.

Species lifespan is, however, correlated with several anatomical and physiological variables, and these are in turn intercorrelated. To clarify these interrelations, we carried out a multiple regression analysis of the dependence of species lifespan on six variables. Two of these could be dropped, and we ended up with a multiple regression relationship of lifespan, $\underline{L}$, to four variables, brain weight, $\underline{E}$, body weight, $\underline{S}$, specific metabolic rate, $\underline{M}$, and body temperature, T_b (Sacher, 1976). The four variables $\underline{E}$, $\underline{S}$, $\underline{L}$, and $\underline{M}$, were given in logarithmic units, because the relationships among these variables are linearized by the logarithmic transformation. Body temperature, T_b, in degrees Celsius, was not transformed. The least squares regression relation is

$$\log L = 0.62 \log E - 0.41 \log S - 0.52 \log M + 0.026\, T_b + 0.894 \qquad (1)$$

The squared multiple correlation of log $\underline{L}$ with these four variables is 0.82.

This analysis shows that species lifespan varies as the minus one-half power of specific metabolic rate, independent of body weight, brain weight, or body temperature. This result gave me a strong incentive to discover how the longevity of individual animals and genotypes within species depended on body weight and metabolic rate.

To examine these relationships, we developed a physiological monitoring system that enables us to measure oxygen consumption, motor activity, and body temperature almost continuously on individual mice for periods of up to a week or more (Sacher and Duffy, 1978).

Regarding the daily cycles of metabolism, motor activity, and body temperature, our data show that there is a remarkable reproducibility of an animal's pattern from day to day, so that every animal has its own "signature." When we follow these animals into old age, it is apparent that the 24-hour average metabolic rate decreases, the resting metabolic rate also decreases, and the motor activity decreases even more. The consequence is that the difference between the average and the minimum metabolic rate values is smaller in old mice, and the day-night cycle is almost abolished. However, old animals, despite the fact that their average metabolism is down about 30 to 40%, seem to be able to maintain their youthful body temperature, presumably by changing their activity patterns, and by decreasing their thermal conductivity and hence their rate of heat loss to the environment.

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*Deceased.

I shall here summarize our findings on the relation of lifespan to body weight and metabolic rate for 85 laboratory mice of 21 inbred and F_1 hybrid genotypes (Sacher and Duffy, 1979). Two relationships were observed in this within-species sample that confirm the relationships previously observed between species of mammals. First, genotype lifespan has a positive, approximately four-tenth power, dependence on adult body weight; second, genotype lifespan has a negative, approximately one-third power, dependence on specific metabolic rate. These two relationships are probably expressive of a single size-and-metabolic factor, because body weight and metabolic rate have a high negative correlation and would be expected to have oppositely signed relations to lifespan. The same-sign relation between species in (1) is a result of the multiple correlation process and indicates that there are independent factors for body weight and metabolic rate between species. However, the simple regressions of log lifespan on log body weight and log metabolic rate between species are positive and negative, respectively, the same as for the simple regressions within species.

The inverse relation of individual lifespan to metabolic rate implies that an increase of energy expenditure by an individual decreases his expectation of life. Such a relation is postulated for the human species in the so-called "rate-of-living" theory of Pearl (1928) and Rubner (1908), which was based in part on the interspecies relation of lifespan to metabolic rate, first described by Rubner (1908). The within-species data on mice described previously are the first direct evidence that there is a negative rate-of-living term governing individual longevity. It is now important to know in what specific way this relationship applies to individual human beings with different levels of energy metabolism, or to a single human being who changes his level of energy metabolism.

There is another relation of genotype lifespan to metabolic rate that is orthogonal to, and hence independent of, the negative linear relation of log lifespan to log resting metabolic rate. The 24-hour average metabolic rate is the sum of the resting metabolism plus the average over the diel cycle of the metabolism in excess of resting, that is, the metabolism of activity. I therefore calculated for each 48-hour data set on each mouse an activity index (AI), which is the ratio of the 24-hour average metabolic rate to the 24-hour minimum, or resting, rate. The AI decreases with age, because the metabolism of activity decrement is about 50 to 70% over the lifespan, whereas the resting metabolism decreases by only 10 to 20%. More interesting, the AI at a fixed age varies significantly between individual mice and between genotypes, and we have been able to show that there is a <u>positive</u> correlation between AI and length of life for individual mice. This leads me to hypothesize that the AI is a measure of health status, or vigor, in quite general sense, perhaps having to do with the energetic efficiency of the animal, that is, his ability to convert ingested energy into useful work. It is defined by the ability, or rather the readiness, to do physical work; but by hypothesis the significance of the AI is that it also is a measure of the ability to do chemical work, such as biosynthesis and immune responses, and also psychic work, such as learning, discrimination, and goal-oriented behavior.

To summarize, the mice data show that there are two metabolic terms relating to individual longevity. One is the classical rate-of-living term, which yields a <u>negative</u> association between energy expenditure and length of life. The other is the activity index, which gives a <u>positive</u> association between the metabolism of activity and individual lifespan (ref. 3).

The interplay between these two factors could easily become quite complex, and even more so when additional factors of body weight, body composition, type of activity, etc., come into consideration. Nevertheless, I believe that these findings make possible the initiation of a national research program on the relationship of health and longevity to the genetically endowed and environmentally conditioned factors that govern the ability of the organism to utilize metabolic energy.

One important question, for example, is whether an increase of AI brought about by training, analogous to the added exercise in a fitness program, is associated with an increase of subsequent lifespan. In regard to spaceflight, is a decrease of AI under weightlessness associated with a decrease of survival?

DISCUSSION

MEITES: You mentioned also the effects of brain weight on longevity.

SACHER: The role of the brain is very enigmatic. Big-brained animals live longer, and one can postulate that the brain is sitting there doing all kinds of good things for us, such as carrying on all the physiological integration processes, but one cannot prove that. As a matter of fact, some physiologists will say that a rat has as good a hypothalamus as a human being, and there is no way of denying it at the moment. Nevertheless, the data show big-brained species like monkeys and people live longer. However, there is another way to look at this problem, and that is in terms of the reproductive cost associated with a large brain. The answer to this is unequivocal: all parameters of reproduction get depressed as species brain size increases — litter size goes down; gestation time and maturation time goes up; there is a longer interval between litters, etc. (ref. 6).

This implies that an increase of brain size must necessarily be accompanied by an increased reproductive span and hence an increased lifespan to maintain an adequate rate of increase per generation.

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THE NEUROENDOCRINE SYSTEM AND AGING

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Since we are supposed to discuss some neuroendocrine approaches, perhaps it is worthwhile to summarize some basic concepts. As you know, the neuroendocrine system controls many body functions, such as growth, reproduction, thyroid and adrenal function, carbohydrate and fat metabolism, mineral metabolism, including phosphorus, etc. Of particular interest is the fact that the hypothalamic portion of the brain produces neurohormones that regulate the function of the pituitary, which in turn controls most of the endocrine organs. All environmental stimuli act via the brain and reach the hypothalamus, stimulating the release of hormones from the hypothalamus, pituitary, and target organs. For instance, in the case of exposure of an animal to low temperatures, the temperature-sensing nerve cells in the skin send impulses to the CNS and hypothalamus, resulting in release of TRH, which acts on the pituitary to release TSH; this in turn acts on the thyroid to stimulate secretion of thyroid hormones (thyroxine and triiodothyronene).

There are at least two types of neurons in the hypothalamus which regulate the function of the anterior pituitary. One type is the peptidergic neuron which secretes TRH, LHRH, etc. The other type produces neurotransmitters, such as the biogenic amines, norepinephrine, dopamine, and serotonine, which play an important role in regulating the secretion of the hypothalamic peptidergic and pituitary hormones. These aminergic neurotransmitters act on the nerve cell body or nerve terminals of the peptidergic neurons to stimulate or inhibit the release of hormones from the hypothalamus into the pituitary portal vessels.

We have been interested in the role of the neuroendocrine system in aging processes, with emphasis on the decline of reproductive function, using rats as a model. We have observed that there are alterations in the estrous cycle of female rats which first change from regular 4-5 d cycles to irregular 7-10 d cycles. This age-related alteration begins at approximately 8-15 months of age. The aging female then enters a constant estrous condition, that is, the follicles in the ovaries develop but the animal does not ovulate. Some rats become pseudopregnant, and the ovaries show corpora lutea which produce progesterone. In the oldest rats, 2 to 3 yr of age, the ovaries shrink, become atrophic, and become functionally inactive.

The male rats show an age-related decrease in spermatogenesis and testosterone production. Blood serum radioimmunoassays of hormones in old male and female rats show a decrease in the levels of LH and LSH, which control gonadal function, and an increase in prolactin, which stimulates development of mammary and pituitary tumors. There also is a decrease in serum testosterone levels and in thyroid function. The changes in reproductive function are related to hypothalamus alterations, since the hypothalamus is the overall regulator of reproduction. Neurotransmitter measurements performed on the median basal hypothalamus show lower levels of norepinephrine and dopamine in older rather than in younger rats. The turnover of these neurotransmitters also is decreased. We also have observed an increase in the turnover of serotonine. These changes in neurotransmitters are believed to partially account for the reduced capacity to secrete gonadotropins and for the increase in secretion of prolactin in aging male and female rats, since catecholamines normally stimulate gonadotropin release, and serotonin inhibits gonadotropin release.

Because aging is accompanied by a decrease in hypothalamic catecholamine levels and by an increase in serotonin, it is possible, by experimentally changing the concentrations of these neurotransmitters in the brain, to reverse certain of the aging changes in reproductive function. By administering appropriate brain-active drugs and by direct hypothalamic stimulation, we have been able to induce regular cycles and pregnancy in some old female rats that had ceased to show estrous cycles. In effect, we have been able to at least partially reverse the aging changes in reproductive function in old female rats.

Another important effect of aging is the difference in response of the neuroendocrine system to environmental stimuli. This can be shown by exposing young rats (3 to 4 months old) and older rats (24 to 28 months old) to a low temperature (4°C (39°F)) for 2 hr. The resulting drop in body temperature is much more marked in the older animals and they show no increase in thyroid function. The young rats, on the contrary, show a considerable increase in blood thyroxine and only a relatively small decrease in body temperature.

Important changes occur in regulation of neuroendocrine functions during aging, as already stated. There are also changes in the pituitary, gonads, and reproductive tract. The pituitary exhibits less capacity to respond to gonadotropins and the thyroid to TSH. The reproductive tract may be less responsive to stimulation by gonadal steroids.

It is of interest that despite the cessation of regular estrous cycles by the aging rat, it is possible to reinitiate cycling and even to induce pregnancies in old female rats by appropriate stimulation of hypothalamo-pituitary function. The cause for the decline in reproductive function in the rat lies in the hypothalamo-pituitary system and not in the gonads, which are potentially capable of function for the life span of the animal.

It also is important to consider that the neuroendocrine system is responsible for regulating many of the metabolic functions of the body and that any effects of weightlessness or stress during spaceflight would necessarily be exerted via the neuroendocrine system. Therefore, it would be important to determine the effects of spaceflight on any changes that may occur in hypothalamic neurotransmitters, hypophysiotropic hormones, and on secretion of pituitary and target gland hormones such as the thyroid, adrenals, and gonads. Insofar as I have been able to determine from the reports presented at this meeting, only fragmentary results are as yet available on the effects of spaceflight on the endocrine system and practically nothing on their effects on the hypothalamus.

DISCUSSION

COMFORT: I saw a couple of reports indicating that L-dopa may be able to reinitiate menstruation in older women . . . (Kruse-Larsen, C.; and Garde, K.: 1971, Lancet, 1: 707; Homykiewicz, O: 1966, Proc. 2nd Symposium Parkinson's Disease Res., New York, Raven Press).

MEITES: I don't know about this in women, but we have shown that many types of stimuli are able to reinitiate cycling in old female rats. We reported several years ago that L-dopa, ipronïazid, epinephrine, progesterone, ACTH, and other stimuli can induce resumption of estrous cycles in old female rats. There are several reports indicating that catecholamines may be deficient in the brain of aging human subjects.

COMFORT: This was the justification given for the utilization of procaine in geriatrics as an antidepressive, because of its effects as a monoamine oxidase inhibitor.

MEITES: The reproductive state of postmenopausal women is very different from that found in rats. In postmenopausal women the ovaries become inactive, fibrotic, and lose their follicles and ova. The ovaries in such women become unresponsive to gonadotropic stimulation, whereas in the rat the loss of reproductive capacity is due primarily to changes in the brain, and can be reversed by appropriate brain treatment with drugs and hormones, as already mentioned. Even the tiny atrophic ovaries of very old rats can start functioning again when transplanted into young ovariectomized female rats.

SHOCK: Catecholamines may be important in the aging of other organs besides the brain. For instance the inability to increase heart output in old age may be related to the important role of catecholamines in the heart tissue.

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COMFORT: We can initiate the discussion by taking a look at a diagram of time-linked processes in the aging organism (fig. 1). I am of the opinion that, in the metabolic area, some useful information can be obtained by exposing animals to zero-g. There are a number of deleterious processes going on in the body, some of which appear to be autonomous, whereas others are subject to some kind of central regulation. The genetic characteristics of the individual play an essential role in determining the subsequent events leading to senescence. In this respect, DNA repair apparently plays a critical role. Metabolic variables are also implicated in the aging process. Another factor is body size, which is interrelated with the "genetic set" and with caloric intake. These last parameters, in addition to growth and development, are clearly related to senescence mechanisms, as shown by the fact that their manipulation alters the rate of aging as expressed in life-table modification. It may be that all these processes are controlled by some kind of "in-flight computer" which sets up the rate of deterioration; or, conversely, the central clock, when certain mechanisms fail, may activate backup mechanisms of various kinds. The central clock is the neuroendocrine system, discussed in previous sessions by Dr. Meites and Dr. Samorajski. As I have indicated by the arrows in my diagram, the neuroendocrine clock is influenced by dietary factors, such as tryptophane intake, and by "size" or caloric intake or both. This is exemplified by the fact that at the

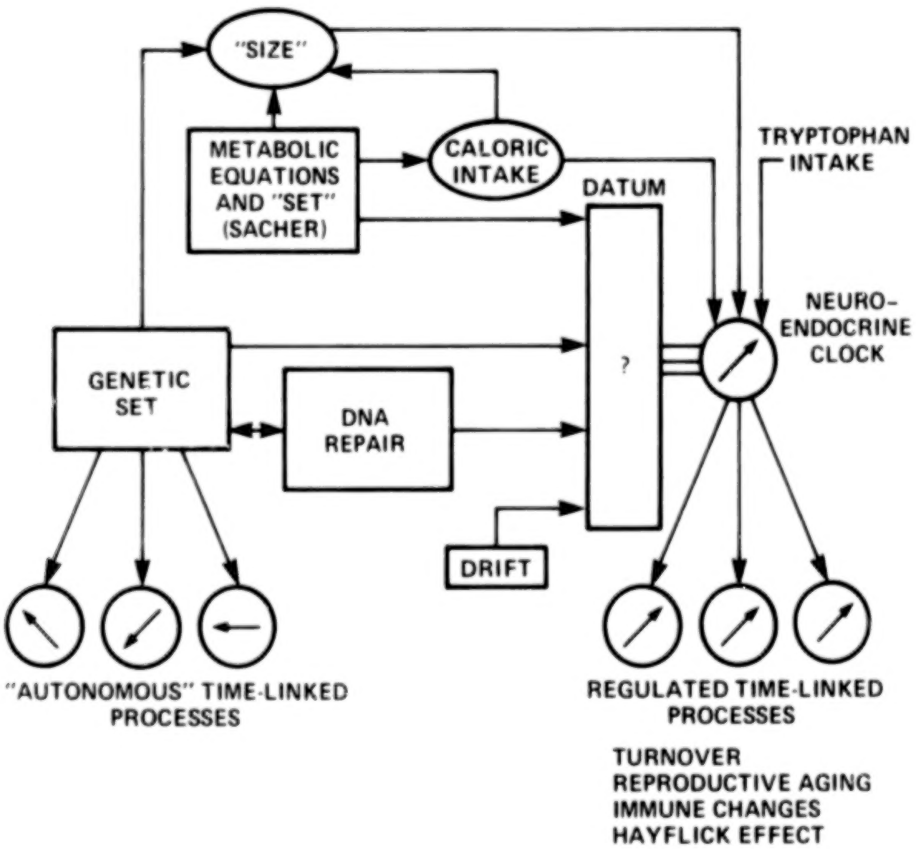

Figure 1.- Systems model of the components of life-span regulation in mammals.

onset of female puberty, menstruation starts when the body reaches a certain mass. Then, if subsequently there is body weight loss, menstruation stops, to start again after enough weight is gained. Thus, we can assume that weight or mass can be "read" somehow during the course of development. Probably there is also some drift which influences the processes occurring in the datum box (fig. 1) controlling the neuroendocrine clock. As George Sacher has pointed out, weight, lifespan, and metabolic rate are all integrated in that datum box. Whether the integration is done primarily by the genetic information or by the genetic information through some depending machinery in the endocrine system remains to be investigated.

In my opinion there are two types of experiments to which weightlessness can contribute. One type is [illegible]ned with the elucidation of various equations that relate the variables ind[illegible]my diagram. The other deals with obtaining information about the way in [illegible]loric intake, and other variables are read by the sensing mechanism, i[illegible], in the brain. The problem of circadian rhythm decay, which has be[illegible] by George Sacher, also fits here, since these biorhythms are modulated to a [illegible]extent by the datum box.

My diagram is only tentative. I want to stress that we should not commit ourselves to a cast-iron hypothesis that the thing to look at is metabolic aging or neuroendocrine aging. I believe that we should keep in mind the whole picture.

We have not said anything at all about the general medical consideration of geriatrics in relation to bed rest or to manned flights to be performed in the future. I have left this out because I wanted to concentrate on the fundamental biology of aging. However, if we are going to set up a working group on space gerontology and geriatrics, then we could address ourselves to those medical topics.

I am immensely impressed by what the NASA program has already accomplished under the difficult conditions of spaceflight. We should keep in mind that only a very limited number of animals could be used in the weightlessness experiments, and that in the manned flights the astronauts had to perform numerous tasks. Despite this, marvelous data have been already obtained. Now, with the advent of the Shuttle, we have the opportunity of going back and carrying out more refined experiments, doing things more properly and in a more leisurely way.

This is all I wanted to say, besides asking for input from the space biologists and from our gerontology group. Rather than asking for specific experiments, because we will need more time to mull over this, I would like to get your ideas about the relevance of our gerontological concepts from the viewpoint of your space biology knowledge.

MIQUEL: I would appreciate having your input on the following questions: If young and middle-aged rodents are sent into space for investigation of the effects of age on the response to zero-g, which parameters should be looked at? Should we sacrifice some of the animals during spaceflight? Should we take blood samples at various time intervals? Would it be advisable to use mice or rats or both? Perhaps Dr. Meites would like to comment on these points.

MEITES: From the neuroendocrine point of view, and based on our own work, the rat would be more suitable than the mouse, particularly for measuring blood hormones, which I believe are the best indicators of what the pituitary and, indirectly, the brain are doing. The measurements of hormones in the blood are very important and one can't very easily do this in the mouse, which after all may have only a milliliter or two of obtainable blood, whereas in a rat it is possible to get a multiple

blood samples, particularly if the animal is cannulated, and that can be done with a minimum of stress. I would be highly in favor of using rats to obtain blood samples and measure the major pituitary and steroid hormones by radioimmunoassay. Then, if these animals are to be kept at zero-g for 1 wk, one could take blood samples every 2 d or so, and thus we could get a very good picture of hormone secretion in relation to the period of time spent in space. Of course it would be interesting to have at zero-g, rats of different ages and sex: young rats, old rats, male and female rats, if possible, since there are some interesting sex differences, and medium-aged rats. The ages could be 2-3 months for the young, perhaps 6-7 months for the middle aged, and approximately 2 years for the old rats. These comparisons could really tell us a lot about the reaction of old versus young and medium-aged rats to weightlessness. And, if possible, to do a few stimulus-type tests, in other words, to test the ability of young versus old rats to react to different stimuli in weightlessness compared with being on Earth. We could use even relatively mild types of stress, such as immobilization, which is very easy to do on rats. You can tape the animals to cages or wrap a towel around them so they can't move. This definitely stresses them and causes in a matter of minutes blood prolactin, LH, and, of course, ACTH to rise very markedly, whereas TSH and growth hormone levels fall. Again we could compare the reaction of young versus old rats to this stimulus or to other types of stimuli, such as administration of certain central-acting drugs. The responses of young and old animals are quite different on Earth and we don't know what might happen in a weightlessness condition.

This should be the first objective. As I see it, we only have small bits of information on the effects of zero-g on the neuroendocrine system, which were discussed yesterday and this morning, and the information reported in the book Biomedical Results of the Skylab Program.

KLEIN: May I ask a question at this point? I am sitting here listening, trying to put myself in the place of one of our NASA hard-nosed officials. We have had literally thousands of proposals to investigate one phenomenon or another of weightlessness. It seems more or less a fishing expedition to see where weightlessness affects this or that parameter. Do wings grow longer or don't they? Do leaves hang upside down or not? Do they turn red or green? There is an infinite variety of possible experiments to investigate the effects of weightlessness on some biological end-point. Now, I am not clear in my own mind whether this general protocol on the influence of age is somewhat in the nature of one of those fishing expeditions. Are we going to do this to see whether or not there is a change or is there some hypothesis that the answers that we are trying to obtain by doing the experiment will help to test? I would like to press you on that a little bit. Is it just that you are trying to determine whether or not changes occur in blood hormones of rats at zero-g or do you already have a clearly conceived hypothesis based on what we have told you or what you may have even dreamed up? It is important that the hypothesis be strong and that there is some fundamental idea to be tested by doing the experiment in weightlessness.

MEITES: I believe that we need to know which changes may take place in the neuroendocrine system as a result of weightlessness and whether there is any difference in the response of old compared with young animals. The other point is that there was a postulation here, and it's an important point raised at this meeting [see presentations by Jaime Miquel and Angelos Economos], that being in space, being weightless, may have an effect on the aging process. If this is true, I don't see how we can help but learn something important about its effects on the neuroendocrine system and aging. I don't consider this merely a fishing expedition.

COMFORT: My own particular interest lies more in the manner in which the mechanisms in the body read the inputs indicated in the diagram I put on the blackboard (fig. 1). It is the only way in which we can do it. We can't do it alone and this is the reason that brought us to NASA. We are asking ourselves whether hypogravity would simulate caloric restriction, because the inputs were read in one way, or caloric overdose because they were read in another way, and there are some critical experiments which we can do along these lines, in the area that George Sacher discussed, on the relation between body size and metabolic rate. It will be very interesting to see the direction of the shifts in some of these parameters, because it will give us a clear-cut choice between two hypotheses on the basic mechanisms of aging. I believe this is very important because it might help us to get rid of one or the other of the two most widely accepted theoretical formulations on the pacesetters of senescence.

SACHER: I am reminded of a controversy of long standing, and very similar in nature, about the long-term biological effects of microwaves. This is a question that after decades of research remains unsolved. The reason may be that we said in a nonspecific way "Let's find out what the effects of microwaves may be," instead of setting up definite reasonable hypotheses about mechanisms, which could be tested experimentally. It is gratifying to note that we are talking today about the long-term "toxicology" of the space environment in more specific terms than were customary in the discussion of the "toxicology" of microwaves. A serious shortcoming of research on microwave bioeffects is that after all this time there are no life-table studies on animals exposed to microwaves. It would be advisable to plan from the beginning a study of the long-term effects of weightlessness. This would not yield the final answer, because some people are not convinced by any amount of evidence, but at least it would give reasonable people evidence about whether or not there are long-term sequelae. This long-term followup is a matter of necessity, because we have no alternative way to validate long-term effects since there is not as yet a generally accepted short-term test that can assure the absence of late injury. We have got to wait a year or more and then do physiological and biochemical studies, or maybe in a worst case wait out the lifespans and look at the morbidity and pathology, or measure the lifetime reproductive performance.

COMFORT: The long-term effects are obviously important, but some concepts can also be tested on short-duration flights. In relation to George Sacher's equations relating body weight to lifespan, I am wondering what happens when we place an animal in weightlessness. We know that if we fast a rat, it loses weight and lives longer. I would like to know what will happen when you artificially reduce the body weight in space or increase it on the centrifuge. I am of the opinion that this may allow some theory-testing.

KLEIN: This is fine. In relation to this particular area of life sciences, I like the idea that you have an equation or equations that you want to test in space.

MIQUEL: I am impressed with George Sacher's methods to determine simultaneously on mice, oxygen consumption, body temperature, and activity. Perhaps, for practical reasons, since we need a working hypothesis in order to justify a flight experiment, we could propose to test the concept discussed by Angelos Economos and me that the metabolic cost of living in weightlessness is lower than at 1-g. This could be investigated using George Sacher's instrumentation, which I presume could be adapted to the space environment.

ECONOMOS: This touches upon a fundamental problem in metabolism which I discussed this morning. The customary (and classical) notion is that basal metabolic rate is strictly determined by the (passive) heat losses from a mammal to the environment. I indicated that this notion of "mammals are heaters" is not supported by modern observations. I suggested that the animals at their "thermoneutral zone" of ambient temperature lose only as much heat as their cells generate in the process of performing their assigned functions, including self-repair ("counter-entropic" metabolism). Now, in larger and more bulky animals a considerable amount of the utilized energy is expended in the support of posture and form of the body against the pull of gravity. (This agrees with evidence from centrifuge studies by Dr. Oyama and colleagues; they have shown an increase of basal metabolic rate per gram mass.) This can be as much as 20-30% of the daily caloric utilization in man. The percentage will change with body weight, and can be seen as follows. The basic equation of metabolism (as established by Kleiber) is

$$BMR = k.BW^{0.75}$$

where BMR is basal metabolic rate and BW stands for body weight (actually body mass). The "counter-gravity" part of the basal expenditure is, however, proportional to body mass. Thus, for a mouse that part will be almost 2,000 times less than for a man, though the total basal metabolic rate of a mouse is "only" 300 times less than that of a man. Therefore, gravity favors smaller animals, energetically and in an evolutionary sense, because it does not burden them with appreciable energy "waste." In weightlessness, then, the situation will be reversed, and larger animals will have considerably reduced basal metabolic rate. The exponent of BW in the above equation will thus be reduced. Calculation shows that the rat is practically the smallest animal on which reduction of BMR at zero-g could be measured; for a 350-g rat the reduction would be of the order of 1.5-3 kcal/day.

SHOCK: It seems to me that we have basically two kinds of experiments that ought not be confused. One class of experiments will focus on the effects of body size as measured by weight. The other class of experiments will consider the effects of the upright position which brings in a lot of other variables: the hydrostatic fluid pressure shifts, the blood pressure changes, etc. All these factors are related. The common denominator is gravity. It seems to me that we are really asking two sets of questions. For instance, size and weight must influence the way the heart reacts to exercise. But there is also a whole volume of information showing that cardiac output in exercise also depends on whether the subject is sitting up on a bicycle or lying down on a bed or walking on a treadmill, even though the work output is kept constant. Now, focusing on the formulations discussed here, we have a series of hypotheses that must be tested in terms of both long- and short-term effects. The long-term effects may be difficult to assess. On the other hand, there are short-term factors that seem to have a bearing on the total question. Namely, if we remove the perception of gravity, what are the immediate effects on physiological functions such as heart rate, blood pressure, and oxygen uptake? Such experiments could be conducted on both humans and experimental animals. However, short-term effects from the removal of gravity might or might not have an effect on total lifespan. Hence, the ultimate answer to this question will require long-term experiments.

KLEIN: This is not excluded, by the way . . .

SHOCK: Well, I think one of the most effective indices of the level of metabolic activity in an individual is the heart rate. Hence, we should monitor heart rate continuously and then superimpose, for example, short bouts of exercise. What is the maximum heart rate that can be achieved? Since all your astronauts are young

healthy individuals, you can ask them to perform at their maximum capacity without worrying about potential risks. If you were dealing with 80-year-old men you would hesitate to ask them to exercise maximally. However, I would like to know the maximum heart rate that can be obtained under conditions of no gravity. Is that maximum reduced?

MIQUEL: I feel that an important parameter in any experiment that we may propose is the oxygen consumption in weightlessness. The data obtained so far in the manned flights of the United States and USSR are, in my opinion, too "contaminated" by psychological factors to allow definite conclusions. Moreover, astronauts and cosmonauts usually had heavy working schedules to avoid deconditioning. Therefore, the results obtained on human subjects may not give an accurate impression of the metabolic cost of life at zero-g. On the other hand, the USSR data on rats flown in biosatellites may have been influenced by psychological stress. I suspect that mature animals fully adapted to zero-g might show a lower food consumption rate than their counterparts, maintained at 1-g. And this, in a way comparable to caloric restriction, may result in an increased longevity.

COMFORT: Experiments in weightlessness may give us the information about the sensing mechanisms related to caloric intake and body size. Are those endocrine sensors counting calories, or sensing body weight or developmental processes associated with the number of cell divisions?

MEITES: I believe I forgot to mention a very important aspect of the experiment that I would like to propose. It relates to what Dr. Comfort just said. I think that it will be necessary to kill some of the rats, not all of them, while they are in space, and remove and freeze the brain and bring it back down to analyze hypothalamic neurotransmitters, such as the biogenic amines and the hypothalamic hormone-releasing factors, to see what changes occur.

COMFORT: Wouldn't an entirely negative result be useless?

MEITES: I can't conceive that you would get entirely negative results. The hypothalamus is after all, related to everything you people are talking about . . . take for instance the control of appetite. As you know, the influence of catecholamines on regulating appetite is very profound. Also, the regulation of body temperature, body metabolism, body growth, and reproduction resides in the hypothalamus.

SAMORAJSKI: There are some very interesting hypotheses in psychiatry that relate to schizophrenia, mania, depression, etc. For example, changes in dopamine, possibly interacting with GABA, may be implicated in schizophrenia. Now, there is some indication that the dopa system is changing in weightlessness, as suggested by some of the prolactin data from the astronauts. I think that it would be very important to look at the hypothalamic biogenic amines in weightlessness and see how they relate to behavior, longevity, and the many other parameters already discussed at this meeting.

MEITES: This can be related both to stress and to the aging process. There are many changes in the brain with aging, some of which are associated with alterations in hormone production, in body metabolism, in reproductive function, and so on. I have been wondering all the time just what relationship stress may have to weightlessness. Is weightlessness a form of stress? In terms of reproduction, we know that stress affects reproduction. In rats under chronic stress, there is a decrease or cessation of reproductive function, an increase in prolactin secretion, and a decrease

in TSH-thyroid function and GH secretion. These would produce very marked metabolic changes in the body.

COMFORT: Weightlessness may in fact amount to a withdrawal of stress, once the subjects have adapted to the space environment. Apparently, astronauts enjoy some of the sensations associated with life at zero-g, even if other sensations might be definitely unpleasant. If you send into space people with impaired muscular function, they may enjoy a freedom of movement that they cannot have at 1-g.

MEITES: I agree with the idea that the results of weightlessness and of psychological stress may not be exactly the same . . .

COMFORT: At zero-g, you are taking some load off the heart and the skeletal muscles . . .

MEITES: And maybe putting some additional load elsewhere . . .

COMFORT: Precisely.

MIQUEL: I believe that if we could have a number of mice in space, it would be worthwhile to look at the effects of weightlessness on the rate of aging. Unfortunately, the planned exposure to zero-g in the Shuttle flights will be only for 7-13 days, which is too short for answering questions of gerontological interest.

SACHER: One possible way to use these brief exposures to weightlessness to get an idea about the effect on aging would be to find out how the rat perceives the situation. I am thinking about an operant test situation in which the animal has the option of choosing between weightlessness and an artificially simulated gravity environment. In other words, how much work is it willing to do to get back into a fractional-g rotating field?

KLEIN: The Russians, this is interesting to note, are proposing a 1980 flight in which rats will be allowed to select along a gravity gradient what g load they feel most comfortable in between 0 and 1-g. We assume this will require the use of a long-arm centrifuge.

SACHER: As I pointed out in my presentation, my research on the genetics of energy metabolism and longevity in mice shows that the lifespan of an individual mouse has a positive correlation with a particular metabolic variable, which I call the Activity Index, namely the ratio of its average metabolic rate over 24 hr to its resting metabolic rate.[1] This variable is really the ratio of the metabolism of activity to the resting metabolism, and it is presumably a function of such parameters as the striated muscle mass, the number of motor nerve cells, and possibly the bone mass. If the Activity Index diminishes, we can predict that the lifespan will be shortened. This offers the possibility that the Activity Index might have predictive value if there is an irreversible loss of muscle mass or neuromuscular function as a consequence of spaceflight.

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[1]Sacher, G. A.; and Duffy, P. H.: Genetic Relation of Lifespan to Metabolic Rate for Inbred Mouse Strains and Their Hybrids. Fed. Proc., vol. 38, 1979, pp. 184-188.

KLEIN: Dr. Sharp probably comes as close as anyone in the room to being a behavioral expert. So if there are any questions on the subject of stress . . .

MIQUEL: Well, we were wondering: Is weightlessness stressful, yes or no? More specifically, if we put mice or rats at zero-g, after 2 or 3 days of being in space are they going to be stressed or might they actually enjoy their "exotic" environment?

SHARP: I don't know if you can tie stress to the space experience, but if you used the notion that a stressed animal is an active animal, then I guess that you could say it is not very stressful. The activity measurements taken are certainly not markedly different from animals that are kept in a similar cage on the ground. If you use the concept of stress as related to the adrenal cortex (hypertrophy, indicating a chronic kind of stress), there is some indication that the spaceflown rats have been slightly stressed. This is based on rats that were exposed to weightlessness in the USSR Cosmos series, and were examined upon return to Earth. If you use as a criterion of stress ulcer or pre-ulcer patches in the stomach and duodenum, there is no evidence that they occur. Food intake data, while very rough because of the way this study was done, suggest that the rats were eating adequately, and I guess that this may be relevant to the problem of stress. But it depends on the dimension of your definition of stress.

COMFORT: I don't like this term. I think that stress is one of these things which, like Freudian sexuality, keeps expanding so much that in the end, they do not mean anything. It seems that we have expanded stress to mean any input into the system. I rather would look at weightlessness as an unconventional challenge to the homeostatic system. I would rather call it a stressful environmental factor.

SHARP: Of course, Selye first posed the notion that any change, any novel change in the environment of an organism, would be reflected in some endocrinological change and responsiveness of the animal to that novel environment. In that definition, obviously, spaceflight would have to be considered stressful. But if you look at it carefully, you may come to the conclusion that such a definition is a tautology. That, in fact, you are just chasing it around and around, and I think when you take Selye's approach to stress and put it in the context of spaceflight, you don't really get very far.

COMFORT: I am of the opinion that we should look into the physiological responses to a particular kind of environmental challenge. In the work that we are planning, we had better forget about stress and describe what is actually happening.

SHARP: I couldn't agree with you more.

ECONOMOS: It is important to consider not only the quality or kind of change, but also its magnitude and how this measures up with limits of capacity that have evolved in an organism. Thus, if you stretch a piece of elastic material too far or for too long, it may break, while a milder and short-lasting stretch may not leave any signs of "stress" behind. Clearly, in this case it's the magnitude of the "change" that is very important, and so it is with an organism. If the change is strong enough and lasts long enough, it may bring one or the other homeostatic systems of the body far out of its dynamic range of normal operation and the organism would be under stress. Thus, the concept of stress is somewhat restricted in this way and, therefore, also made more meaningful.

COMFORT: I think, we really ought to separate here weightlessness from the considerable number of irrelevant disturbances that we have to go through to have weightlessness, such as firing rockets, vibration, etc. Even having rats in a centrifuge to increase their weight involves some disturbance, such as noise, acceleration, and things like that.

SHARP: Of course, in the ideal world — and we don't have it — the animals should be conceived and raised in space, at zero-g.

COMFORT: Well, this is a possibility if we could have long-duration flights but we are talking at the moment about doing 7-day experiments. It would be nice to have spacelab operations going on for about 2 yr or longer; then we would study the complete aging process of a mouse or rat.

SHARP: If you could investigate an animal with a lifespan that is within a short flight duration, you might design experiments to utilize the Spacelab.

COMFORT: The only practical approach would be to use annual fish, which usually do not live as long as the smallest mammals. However, there is a great problem in working at zero-g with fish . . . fish adjust to hydrostatic pressure by means of the swim bladder . . . it would be better to hatch fish in weightlessness.

SHARP: Well, we have come close to that with fish in an Apollo experiment. What that experiment led to was another experiment done in Skylab, where mature fish were taken into space and observed there. Incidentally, it wasn't a formal experiment, it was a NASA demonstration project and it was found that the animals seemed, after a short time, to orient to light. That is, they would put their back to the source of light. If the light was on the floor, they would swim upside down. But with any agitation, presumably due to kinostatic or proprioceptive or vestibular disturbance, they lost the ability to do this and chose some very peculiar swimming behavior best described as looping. After one stopped shaking their aquarium, they would slowly come back to orienting themselves relative to the light position.

COMFORT: Mammals would be, of course, more suitable. However, we simply do not have any good model with a shorter lifespan than the mouse.

SHARP: Nevertheless, it might be that fundamental processes exist in aging that can be generalized from animal A to animal B, up to man. Is it not likely that there are general mechanisms of aging, whether in a fruit fly or a bean sprout? If you attack that fundamental problem by using a model that fits the constraints of the Shuttle flights, you may be able to solve some important problem.

COMFORT: There are, in fact, curves which show that some common fundamental principles may apply to the aging of biological creatures, the Roman Empire, and motor cars. However, I think that we are now beginning to look at the actual systems operation of aging of the animal which concerns us, which is man.

SHARP: Still, some people are interested in mice, for the mice's sake.

COMFORT: I would like to see a 10-yr-old mouse, but the most important question is how to manipulate the human aging rate. Numerous single-cause or fundamentalist theories of aging have been proposed. However, I am hearing less of those types of theories and far more of the concepts drawn on the board. For this reason, I would not like to get trapped into doing experiments dealing exclusively with lower animals.

SHARP: Well, there is another way to attack the problem, although you have to recognize that it is a long-range attack, a strategic rather than a tactical approach. If you have some solid scientific reasons you could mount an effort from within NASA and from without NASA to bring pressures to bear for long-range facilities. It is absolutely ludicrous that NASA will not plan to fly a laboratory for a longer duration than 30 days. There is no a priori reason why NASA can't be told: "You have to fly us for 6 months or 6 years or whatever the duration is."

COMFORT: If NASA is serious about setting up long-term space colonies, I imagine that people here will also start thinking very seriously about the implications of very long exposure to weightlessness on the aging process.

SHARP: If by exposing mammals to long-duration zero gravity you could contribute toward answering some important question about the aging process, you would have every reason in the world to turn this country loose on that kind of a problem, and it would be legitimate, if you could convince enough people that you will answer such questions. You know it is similar to the astronomers who say they have to go into space to get above the atmosphere to peer at that twinkling star, and if they go they will tell us more about that star. Such arguments seem to convince everybody of importance in the decision process.

KLEIN: Perhaps you could now sit by yourselves and see if you can reach a decision about the possibility of getting involved in the planning of flight experiments with some relevance to gerontology.

COMFORT: I believe that the answer is yes, that there is a consensus that if we do a little more soul-searching, we can devise some experiments to get important answers. The two general approaches seem to be the problem of body-mass sensing in weightlessness and the effect of weightlessness on metabolic rate and related variables, which may play an important and not yet clarified role in determining the rate of aging. [A more detailed discussion of space gerontology and geriatrics by Dr. Comfort is presented in appendix D.]

APPENDIX A

A SUMMARY OF SPACE GERONTOLOGICAL IDEAS

Angelos C. Economos and Jaime Miquel

Weightlessness as a tool to investigate the role of the hypothalamus as a possible pacesetter of senescence, body weight, and lifespan.

1. One of the most vividly debated ideas in gerontology these days is that the aging rate in mammals is set by a central clock or "in-flight computer" (presumably located in the hypothalamus). Does this "computer" read body weight as contrasted with body mass, or does it simply count ingested calories? If body weight is read, then weightlessness would affect the "clock" and the aging rate.

2. Two decades ago, Sacher described an empirical double-logarithmic relationship between lifespan and body weight based on data from 60 mammalian species. On the other hand, if a rat is fasted it loses weight and lives longer. The question arises: What will happen when you artificially reduce the body weight in space?

In considering these hypotheses, the following comments appear to be pertinent.

1. What part of the concept could be tested on the centrifuge? For instance, from the fact that onset of menstruation coincides with attainment of a certain body weight, within the proposed framework it should be expected that sexual maturity would be delayed (indefinitely?) in weightlessness and speeded up in hypergravity. However, the latter is apparently not true in rats.

2. If body weight were sensed, would the generated signal be proportional to body weight? This would be reasonable but would cause difficulties in the outline of the expected effects in the weightless state. For, if the generated signal triggered a certain process in the body, in weightlessness the signal would be zero and the process would not be stimulated at all. This may lead to "peculiar" deductions. For instance, if the body weight control system read body weight and not mass or another variable, then at zero-g the feedback signal would disappear and the animal would be in an open loop of continuous hyperphagia.

3. When relationships involving body weight (BW) as one of the independent variables are proposed to be tested in weightlessness, one should clearly understand if BW actually represented something else, such as body mass or geometric dimensions. Some confusion is caused by the fact that BW has been used very indiscriminately in the biological literature, understandably, if one considers the constancy of Earth's gravitational force. For instance, it was proposed to test Sacher's well-known equation that relates the lifespan of mammals with their body weight. However, it is not the body weight but the body mass of the animal that enters Sacher's equation. (This, again, is not entirely correct, because body mass here is to a large extent a substitute for dimensions, particularly body surface.) Clearly, one should distinguish between "metabolic body weight," so to speak, and mechanical "body weight." For instance, if an animal is fasted it loses weight and lives longer; however, a smaller weight in Sacher's equation corresponds to a shorter lifespan.

4. In a control system, sensors are needed for any variable that changes with time. Body weight does change during development and during normal life. However, body weight consists of the component's mass and gravitational acceleration; the second is constant. It is not clear why the metabolic systems of the body should sense gravitational load per se, which is constant. (The effect of weight on the skeleton is a special case.) However, even body mass per se is probably not monitored, but some function of caloric content and intake is measured instead: maybe fat content of the body as reflected in lipid levels, because the fat deposits represent the largest store of utilizable energy in the body. It would be difficult to imagine a transducer for body mass per se.

Weightlessness constitutes a stress input to the body; therefore, it will speed up the aging process through the neuroendocrine system. Many of the neuroendocrine changes associated with decline of body functions during aging have been uncovered in recent years. The hypothesis can be tested (1) by measuring the effects of spaceflight on hypothalamic and general brain concentrations and turnover of neurotransmitters that regulate pituitary function in young, mature, and old rats of both sexes; (2) by measuring the blood levels of pituitary, gonadal, and adrenal hormones; (3) by measuring the effects on the estrus cycle in females and on spermatogenesis in males; (4) by subjecting three age groups to different stimuli such as immobilization stress, drugs that alter hypothalamic neurotransmitter activity, and dehydration, to test their effects on neuroendocrine function. The results obtained should determine (1) whether the spaceflight-aging hypothesis is correct; (2) the effects of spaceflight on neuroendocrine functions, about which almost no meaningful information is available at present; and (3) the effects of spaceflight on three different age groups, which should determine whether neuroendocrine functions in older rats are more affected by spaceflight than they are in younger rats.

How are neuroendocrine adaptive responses to weightlessness affected by age? Contrasting with the view that the hypothalamus may set the aging rate is the view that the hypothalamus, in its capacity of master controller of homeostasis, may actually act to some extent as a "brake" of aging, at least in the initial stages, by triggering adaptive changes in the neuroendocrine apparatus to counteract degradation with aging. On the other hand, again in its capacity of master controller of homeostasis, the hypothalamus plays a central role in the body's adaptive changes during exposure to weightlessness. Therefore, an interaction between weightlessness effects and aging at the hypothalamic level should be expected.

There are large differences in the state of the neuroendocrine systems of young and old animals, and these differences will affect the adaptive responses of young and old animals to weightlessness. Any environmental change that displaces variables of the internal environment beyond their evolutionarily programmed "normal" dynamic range (and thus, in our view, constitutes a "stress"), markedly affects the neuroendocrine systems, presumably in a different way in young and old animals. Does weightlessness cause "stress-reactions" in the neuroendocrine systems, particularly at the hypothalamic level? Or does the elimination of the gravitational load in weightlessness trigger favorable neuroendocrine changes, not excluding a possibility of "rejuvenation" of levels of hypothalamic neurohormones and neurotransmitters in old animals?

Hypotheses with psychiatric-geriatric overtones. There is some evidence from Skylab that spaceflight may affect the levels of neurotransmitters in the brain (such as dopamine and GABA), in ways that may resemble changes involved in various abnormal mental conditions (such as schizophrenia and depression). This needs further investigation.

The rate of aging will be reduced in weightlessness as a result of reduced metabolic cost of living in the weightless state. Naturally, this hypothesis could be tested directly only by means of long-term exposure to weightlessness, ideally by actuarial studies. Time-condensed nonactuarial techniques are currently under development, which may allow tests of this hypothesis in mice over a period equal to 6 months (less than one-fifth of the average lifespan). More important, there are some indirect tests of the hypothesis that are realizable in short-term space experiments (on board the Space Shuttle).

1. Overall oxygen utilization by a mammal will be reduced in weightlessness. The smallest mammal in which a change can be measured is probably the rat. Larger animals will benefit more than smaller ones, homeotherms more than poikilotherms. The exponent b in the relationship $BMR = K\ BW^b$, where BMR is basal metabolic rate and BW stands for body weight (actually mass) will be reduced in weightlessness.

2. However, some internal organs may have a higher rate of living in weightlessness because of being involved in the support of the adapted state of the organism. For instance, the kidneys may work harder and so may the heart (if heart rate will stay elevated over long periods). This may reduce the "lifespan" of individual organs by increasing thermodynamic wear-and-tear, thus affecting the organism's lifespan. In the mouse, 2 wk of life correspond to 1 yr of human life, so that processes in this mammal may be affected despite the short exposure to weightlessness.

3. For example, the developmental (growth) process may be significantly affected in the mouse, because 2 wk in the first period of life after birth in this mammal correspond to about 25% of the total growth period. Growth may be accelerated by weightlessness, which will have deleterious effects on lifespan, according to a gerontological hypothesis which relates rate of aging with speed of development. Some related ideas are expressed in (4) and (5) following.

4. There is a hypothesis that states that in humans, because of blood shifts in weightlessness, fluid is lost and red cells have to be lost too to avoid increase of hematocrit. Still, the loss of red blood cells may be primary, a result of the induced hypodynamia. This can be tested in a quadrupedic animal in which there should be minimal fluid shifts. It should be, however, an animal that is large enough for the metabolic effect of the disappearance of gravitational load to be measurable (rat or larger animal).

5. Does metabolic efficiency change in weightlessness? How does caloric intake versus O_2 consumption in weightlessness compare with ground controls?

Comment. The Space Gerontology Group fully realizes that, in accordance with general scientific practices, the ideas to be tested in space should be sound and fundamental, the hypotheses strong, and the indispensability of the space environment indisputable.

Particularly because space-gerontological experiments are being planned for the first time, there is so much one would like to know on the adaptive responses of young versus old animals upon exposure to weightlessness. A tendency to plan "fishing" types of experiments should, however, be restricted.

Nevertheless, sometimes it may be difficult to set the demarcation line between a "fishing expedition" and a scientific hypothesis-testing endeavor. Undoubtedly, a "fishing expedition" could be reformulated to appear like hypothesis-testing by stating not that one is interested in changes in this or that parameter, but that one wants to test the hypothesis that this or that parameter will undergo this or that change. It seems to us that the criterion should be at a deeper level; it should be demanded that what one is looking for should be scientifically sound, interesting, important, or even useful.

APPENDIX B

TOPICS IN SPACE GERONTOLOGY: EFFECTS OF ALTERED GRAVITY AND THE PROBLEM OF BIOLOGICAL AGE

Angelos C. Economos

ALTERED GRAVITY AS A GERONTOLOGICAL RESEARCH TOOL[1]

Permanent space settlements may soon emerge from science fiction pages into reality. Yet, although the technological problems in constructing a large space structure are in the process of being solved, the important question of how men, women, and children will fare in the space environment during long periods of time, perhaps lifetimes, remains unanswered. This question continues to challenge and elude space biologists. Uncertainties about the capacity of the human body to successfully adapt and remain healthy in the space environment are many. Concerns about cardiovascular deconditioning, muscle atrophy, and bone fragility are well-founded worries. The effect of age on the degree and reversibility of deconditioning changes and the effect of the space environment on the rate of the aging process are also unknown. Even more troublesome, however, is the uncertainty about the body's capacity to readapt to the Earth's environment after a prolonged stay in space. If the deconditioning changes that take place in the space environment reach a point beyond which they are irreversible, the space traveler would then be permanently exiled in space, trapped by the inability of his own body to withstand his native environment.

One solution to the problems of deconditioning is to avoid the environment that produces them. The designers of permanent space settlements have chosen to copy the terrestrial environment as closely as possible; in particular, a gravitational field simulating that on Earth is considered a prime requirement for any design of a space settlement.

Rotating the entire space station to create a centripetal force outward from the axis of rotation is the principal means of producing an artificial gravity for the inhabitants of the space station. Two factors affect the "gravity" felt at any location within the station: the speed at which the station is rotating (angular velocity) and the distance from the axis of rotation. Increasing either of these will increase the "gravitational forces" acting on an inhabitant. While increasing the angular velocity has more of an effect than increasing the distance from the axis of rotation, it also increases the disorienting side effect of other forces (Coriolis) which act on any body in a rotating system. These forces are thought responsible for the symptoms of motion sickness experienced by some astronauts. The chosen solution then is to design a slowly rotating, large-diameter station, primarily to counteract the deconditioning effects of weightlessness.

In our space-gerontological investigation, we are focusing on the artificial gravitational fields of the space station, not as a means of replicating the Earth's

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[1]Presented at the 31st Meeting of the Gerontological Society, Dallas, 1978. I thank Carl T. Reichwein and Jaime Miquel for useful discussions.

environment to avoid problems of deconditioning, but as a unique research tool for probing the role of gravity in the evolution of mammalian body structure and metabolism and, indirectly, in the aging process.

One of the hypotheses in this ongoing study is that insight into long-term effects of weightlessness on physiological functions might be deepened, not only by looking at the short snapshots of data that have only recently been collected in space, but also by looking backward at the evolution of mammals under a constant gravitational field. In addition, the data that have been obtained from studies of animals in centrifuged habitats in which the resultant "gravitational" force has been increased are also analyzed.

Life of Earth has evolved under a virtually constant gravitational field. Those life forms that do not depend directly on gravity for orientation probably possess no specific adaptive mechanisms to cope with altered gravity. Mammals adjust their internal environment to counteract direct mechanical effects from altered gravity, such as body fluid shifts (which occur only in humans, because of orthostatic posture), altered load on the skeleton, and changed muscular work needed to maintain form, posture, and locomotion. This is in contrast to the complex spectrum of active mechanisms they possess to prevent, for instance, change of their body temperature when ambient temperature varies.[2] The existence of these mechanisms makes it impossible to substantially increase the metabolic energy expenditure of these animals by exposing them to cold without causing significant changes in many of their physiological and endocrine functions. Yet, an experimental manipulation of metabolic energy expenditure is required for a direct test of one of the basic theories of the mechanism of aging, the "rate-of-living" theory, which states that the pace of aging is set by a metabolic "clock." Artificial gravity that deviates little from normal gravity (e.g., 25% to 50% lower or higher) may therefore be a "Trojan Horse" to the body metabolism, that is, a tool to manipulate the level of metabolism without triggering active defense mechanisms in the body; thus the rate-of-living theory can be tested in small mammals.

Galileo recognized that larger animals have evolved disproportionately thicker legs to support the increased gravitational load. We have extended Galileo's concept to the physiological function of mammals and have found that the energy expenditure against gravity increases with increased size according to a definite mathematical law derived from data. Larger mammals are at a disadvantage because the proportion of their metabolic energy wasted in working against gravity is considerably larger than that proportion expended by smaller animals.

Analysis of the data indicates that in the centrifuge, a mammal can adapt to a maximum gravitational field that is larger the smaller the animal. Where the limit for a 30-g mouse is 7 times Earth's gravity, for a 300-g rat it is 5 times, for a 10-kg dog it is 3 times, for a 2-kg chicken it is 3 times, and for a 70-kg man it is less than 2 times, probably no more than 75% above normal gravity. Therefore, weightlessness, a 100% reduction of gravity, may be a little more of a challenge than the human body can cope with for a lifetime. Because the deviation from normal gravity may be too strong a challenge to homeostasis, there may be a metabolic cost of living in weightlessness; body fluid shifts may also contribute to this metabolic cost. In addition, in weightlessness moving around costs more energy than it ought to theoretically from disappearance of gravitational load, because loss of contact with the

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[2]By analogy with homeotherm and poikilotherm, one could use the terms homeogravic and poikilogravic.

ground makes it necessary to use muscle power not usually expended on Earth. These considerations are in agreement with the finding that Skylab astronauts (surprisingly) ate as much in space as on Earth.

Based on the above analysis, we may conclude that men and women living in a space habitat with gravity at a 50% or 75% level compared with Earth gravity, would be expected to suffer little disturbance of their internal climate but have a lowered metabolic energy expenditure. (The latter was indeed observed in the astronauts who walked on the surface of the Moon, where gravity is 17% of the Earth's gravity.) With the body's metabolic machinery working at a lower pace, all cells of the body will work at a lower pace (with the exception of the brain cells). Therefore, the aging rate would be expected to decrease and the lifespan to be extended. This is of course purely hypothetical at the present time, but there is a solid base for the belief that in a space settlement with reduced, but not zero, gravity, though not a fountain of youth, a reduced aging rate will be experienced. A reduction of aging rate of about 30% of the reduction of gravity or 10-15% would be expected for man. For a small experimental animal like the rat, the reduction of the pace of the aging process would be about 50% of that for man.

Finally, because hypergravity has a strong inhibiting effect on the rate of growth of small mammals (about 50% at 2-g and 100% at 4-g), it may be an excellent procedure with which to manipulate the lifespans of these animals. Thus, such retardation of growth in the centrifuge may have similar effects, that is, reduced aging rate and significant prolongation of life, as in the classical caloric restriction experiments. This remains to be shown.

RATIONALE FOR A SYSTEMS APPROACH TO ADAPTATION TO SPACEFLIGHT AND DEPENDENCE OF ADAPTATION CAPACITY ON BIOLOGICAL AGE

Introduction

Despite the fact that the body is a system consisting of many organs and subsystems in a harmonious dynamic interplay, research in physiology during the last decades has largely followed a piecemeal approach, treating each subsystem separately, as if it were justified to study a "cardiovascular man" so to speak, or an "endocrine man," and so on. Though this approach may be fruitful under well-defined resting conditions permitting investigation of one particular subsystem in relative dynamic isolation from other subsystems of the body, it is bound to generate more confusion than understanding in the study of physiological responses and adaptation to stressful environments and weightlessness. The reason is simply that when external stimuli deviate from a dynamic range to which an organism has been adapted during evolution, then shifts in many or all internal homeostatic control systems will take place to effectuate the best possible responses, establish new equilibrium points, and thus, combined with reflex or conscious behavioral changes, ensure survival and well-being of the individual within its functional limitations.

Systems Approach to Biology

The methods applied in scientific research are subject to "fashion," as study of the history of various sciences reveals. In the case of the systems approach to biology, though it had been popular in the early 1900s, it was neglected or even

became infamous during the rise of molecular biology (mid-1940s to mid-1960s) (ref. 1). When the limitations of the latter as the sole tool in understanding the body as a whole were (gradually) recognized, the systems approach started to gain respectability once more (ref. 2). In the subsequent years it has become clear that the systems paradigm holds a "great promise for the future" for biology in its perennial search for the principles of function of living beings.

The general systems approach to biology uses and requires information from all levels of biological organization of an individual organism, such as the organ or physiological level, cellular, subcellular, and molecular levels. Within the confines of one level, such as the physiological level, the systems approach emphasizes the need for studying the various subsystems not only separately and under resting conditions, but, most important, with emphasis on dynamic interactions between organs and subsystems, particularly under impinging environmental disturbances. Such an approach has not yet been used, except to a rather limited extent in some of the recent monographs on biological control systems (refs. 3, 4). Constructing detailed models of the physiological systems and their interactions has been proposed and attempted in the past. Generally speaking, the amount of data and assumptions needed to implement such models outweigh the end products, which are questionable at best. A simpler, straightforward approach is needed. Furthermore, the physiological level has customarily been further "dissected" into neuromuscular, cardiovascular, neuroendocrine, and other subsystems, which in turn have their own main subdivisions; as examples, the systems approach has been recently applied fruitfully to the cardiovascular system (ref. 5), and to a major subsystem of the neuroendocrine system, namely the "brain-pituitary-adrenal axis" (ref. 6).

Vitality and Rate of Aging

A study assessing the effects of the space environment on aging, thus laying the foundations for the development of a "space gerontology," would be confronted with the following problem: As yet there does not exist a well-defined, broad-scope method that can be used for defining and quantitating aging and adaptation in any experimental animal or humans. Development and extensive use of such a method in the laboratory is prerequisite to an investigation of the modulatory effects of weightlessness and spaceflight on aging mechanisms and the dependence of astronaut adaptation capacity on biological age.

In an effort directed toward understanding the physiological basis of phenomena at a still higher level of biological organization, namely the mortality kinetics of aging populations (ref. 7), we have applied a quasi-quantitative systems approach, which is summarized here. An animal is viewed as a complex system of interacting organs and subsystems which, in a constant external environment, "cooperate" in establishing a stable internal environment, in accordance with the concepts of homeostasis of Bernard (ref. 8), Cannon (ref. 9), and others. In order to define the "homeostatic competence" or vitality of the animal quantitatively, upon which survival of the individual in a hostile environment as well as in "the" normal environment is directly dependent, we denote by X_j, $j = 1,2...,n$ the functional capacity of the organs and homeostatic systems of the animal that are indispensable for survival in a particular environment. Because, for instance, eyes and ears are important organs for animals in the wild but less so in a laboratory environment, whereas the heart and kidneys are of course of great, though not necessarily equal, importance in both environments, for each X_j we introduce a parameter A_j which is supposed to represent the relative significance of the corresponding organs or

systems for survival of a particular individual. As a linear approximation of the vitality V(t) of the animal at a certain age t, that is, its capacity to resist environmental challenges and death, the following definition-equation can be used:

$$V(t) = \sum_{j=1}^{n} AjXj(t) \qquad (1)$$

It is a tacit assumption in the above analysis that, for equation (1) to have a predictive value, each Xj should represent the total functional reserve of the corresponding organ. However, it can be stated in general, that the customary techniques of medicine are not suitable for measuring this reserve. To mention one example, although a certain individual may show a normal glucose tolerance, that is, a "normal" fasting glucose level and a normal response to ingestion of a standard amount of glucose, the true functional reserve of its glucose control system could be revealed only by more severe tests, such as a "dose-response" curve obtained in a number of sessions with increasing amounts of glucose load or response of the glucose control system to a number of such loads in succession. Another limitation of the rather mild testing conditions presently in use, lies in the fact that the state of various organs or subsystems may obscure the value of an Xj under study because of organ interactions.

The variable t (chronological age) has been introduced in equation (1) because, as it could be expected, the various Xj's of an individual are progressively lowered as the individual ages. It is important to keep in mind, however, that equation (1) gives the vitality of the individual at a certain chronological age but does not predict how the vitality will change with age. Thus, even if two individuals started with the same total vitality and all their organs deteriorated at the same rate, their vitality might not decline at the same rate over a long period of time. This is because key organs of the two individuals, starting with different functional reserves, though being compensated in the beginning by complementary differences in other organs, may reach at different times critical threshold levels below which a real burden is placed on the other organs.

An important implication should be stated explicitly. Because of differences in the genetic constitution or blueprint (i.e., the functional capacities of the organs) among various individuals, any "integrated" parameter of the individuals' physiology (i.e., one dependent on many organs and homeostatic subsystems), for instance the body weight, will possess a stochastic distribution whose form may change with age and whose variance will increase with age. Two conditions will increase this variance in genetically homogeneous populations: (1) exposure of the individuals to different environments and thus to random environmental influences (where environment includes nutrition, smoking, excessive drinking and eating, etc., in addition to what is commonly considered as such), and (2) whether a test is performed in a stressful environment. Such variabilities have become evident in the responses of the astronauts to weightlessness and spaceflight stress and are also a constant worry in physiological research.

The significance of such variabilities as outlined above does not seem to have been generally appreciated in physiological research, where averages and standard deviations of the responses of a number of animals in each test are usually considered and groups are compared by means of various statistical tests. A practical implication of the above discussion is that, in combating or preventing disease, the doctor should approach a patient as an individual and not as a "sample" from an

average population; similarly, pharmacophysiological countermeasures to be developed against weightlessness and spaceflight stress should be tailored to the homeostatic "needs" of each particular astronaut, needs that could be quantitatively estimated by means of dynamic evaluation of the functional reserves of the major organs and subsystems of each astronaut and an understanding, through systems analysis and computer simulation, of the organismic responses to the spaceship environment.

Biological Age

Phenomenological observation of an aging population of individuals who were born simultaneously shows that they die at various ages. We assume that the actual life expectancy of an individual at any point in time will depend directly on his "health state" or "vitality" at that time. Therefore, vitality of an individual at a given chronological age after maturity is a measure of his overall capacity to meet environmental challenges and thus avoid death.

Chronological age is a measure of how long a recognizable entity has been in existence. It is commonly the number of years an individual has lived; it is by no means a measure of his state of health and is a statistically poor estimator of the number of years he has left to live.

Measurement of biological age implies a measurement of the health state of an individual. The focus on the individual rather than a population is indeed appropriate from the humanistic point of view which directs attention to individual astronauts; on the other hand, there will be only a few astronauts on each mission, which precludes the use of the methods of population statistics. Nevertheless, in animal experiments involving small rodents and insects, a sufficient number of individuals can be studied simultaneously to constitute a "population." However, the relatively long duration of lifespan experiments customary in experimental gerontology necessitates a shift of the emphasis from actuarial to nonactuarial time-condensed methods, when the anticipated short spaceflight durations of the Space Shuttle era are taken into consideration.

Pursuing the development of nonactuarial methods for assessing "vitality" in populations in parallel with the development of techniques for determining biological age or "vitality" of individual organisms is advantageous. Clearly, since a population is a collection of individuals, techniques and concepts relating to the determination of vitality at the individual level should be transformable mathematically to those relating to vitality at the population level, the transformation being governed by statistical rules. Moreover, according to established scientific practices, demonstration of an effect of a given agent, environmental factor, etc., such as weightlessness, is scientifically acceptable only if a large enough experimental population has been tested and compared with a similar population of "control" individuals. Therefore, in studies involving animal experiments, "population" methods may have certain advantages based on considerations of simplicity and experimenter time investment.

Aging is characterized by an irreversible degenerating process in which reserve capacity is diminished. Carrying this one step further, the terminal stages of aging result in a situation in which the reserve capacities of the physiological systems are not adequate to withstand the perturbations of environmental inputs and the chance occurrence of an external stress or strong stimulus results in death. This interpretation of aging implies that biological age is a measure of the organism's ability to resist death.

We define biological age B(t) of an individual at chronological age t as its remaining lifespan. Since this is intuitively the best measure of the vitality of the individual at chronological age t, the problem of determining B(t) is replaced by the problem of developing the best statistical method of estimating vitality. This can be broken down into two subproblems:

1. Identify various measurable indices of the physiology, biochemistry, etc., of an individual which undergo changes as the life of the individual unfolds

2. Define the statistically best estimator of vitality as a composite function of these indices

An outline of our approach is as follows. Our point of departure is that the laws underlying the "aging-track" of a given population (i.e., the time patterns of aging processes of the individuals) are constant in a population living under constant environmental conditions. Therefore, by performing suitable measurements in one large population from birth to death of all of its individuals, relationships and "laws" may be established which will be the same for any future population with the same genetic makeup and living in a similar environment.

Any simple vitality index of each individual will decrease with the passage of time and at each time (i.e., chronological age) there will be a definite frequency distribution of the values of any such vitality index. We introduce the notion that if a variety of vitality indices could be combined to give one composite index whose value will reflect the overall vitality of each individual, that value will be statistically well correlated with remaining lifespan, that is, biological age. We further introduce the assumption that a linear summation of the partial vitality indices of the form

$$V(t) = \sum_{j=1}^{n} AjXj(t)$$

where the Aj are parameters to be estimated and Xj are the partial vitality indices, may prove to be a good estimator of biological age.

Practically, our method consists of calculating parameters Aj at each chronological age by means of a multivariate regression analysis of the exactly known (retrospectively) set of values of remaining lifespans and the sets of measured values for the various partial indices. Once these parameters have been estimated for one population, they can be used for "predicting" biological age of an individual of another population at a given chronological age.

Identification of the partial indices of vitality should be pursued by means of a systems analysis of physiological and physiological-gerontological data available for various small animal species and humans. Selection should be based on various criteria, including degree of apparent correlation of an index with aging processes, ease and noninvasiveness of the necessary measurement method, applicability to humans, and, in the framework of space gerontology, suitability for the weightlessness environment.

The necessity of collecting data for one population from birth to death indicates that the most profitable way to commence these studies will be with short-lived species, such as fruit flies. Reasons for using this particular insect have been

repeatedly elaborated in the gerontological literature; they are, among others, short lifespan (maximum of 125 days at 21°C ambient temperature), small size, availability of large numbers of individuals, ease of culture of inbred populations, inexpensive "animal care," and availability of noninvasive methods for measurement of physiological indices of their functions, such as neuromuscular coordination and mating ability. These indices should be assessed for each individual of a given population separately at weekly intervals until natural death. Since these indices are "integrated," that is, dependent on many "lower level" indices of the physiology of the animals, it is possible that they will suffice for the determination of a composite index of biological age. A similar approach can be used for mammals, assuming that a "battery of tests" (ref. 10) has been assembled.

Conclusion

In a nutshell, then, the main purposes of a systems analysis study of adaptation to spaceflight are (1) to identify the (major) adaptive responses of the body at various levels of biological organization (physiological, biochemical, cellular, etc.) and analyze their interrelationships; (2) to pinpoint differences and similarities in the responses between astronauts and experimental animals, particularly rodents; (3) place the main findings of hypodynamic and hypergravity studies in perspective from the point of view of weightless man; (4) analyze the effects of general spaceflight stress versus effects of weightlessness per se; and (5) to formulate tentative hypotheses about the effect of biological age on adaptive responses to spaceflight and the effect of (prolonged) spaceflight on rate of aging, as well as to propose experiments to test these hypotheses.

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APPENDIX C

AGING AND SPACE TRAVEL*

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This paper deals with the matter of aging and its relation to space vehicle crewmembers undertaking prolonged lunar and trans-lunar space missions.

The Mercury Astronaut program imposed an upper age limit of forty as one of the selection criteria for candidates (ref. 18). The background of training and experience required of the Mercury astronauts automatically set a lower age limit somewhere in the late twenties.

Two decades from now, when prolonged manned space probes begin to become relatively common, it may prove expedient to include some non-pilot space crewmembers whose ages may considerably exceed forty. There are many reasons why this is likely, one being the high degree of specialization increasingly required for full mastery of the many complex subsystems comprising the spacecraft (refs. 4, 12). Also, the most highly motivated and most capable individual available for a given position on a given mission may be in his fifth or sixth decade. This may particularly be true if the mission requires an astronomer, exobiologist, or geochemist.

What, then, in consideration of our present level of knowledge concerning the aging process, and its attendant potential infirmities, can we now anticipate to be special problems in what might be called astrogerontology? What assets are likely to be brought by older crewmembers to the realm of space travel?

Following several months or longer under attenuated gravitational forces, or in a state of weightlessness, the cosmonaut will find the return to 1-g life quite stressful (ref. 19). This will be particularly true for the older cosmonaut. Striated muscle intracellular myofibrils will have to be multiplied, a process which occurs more and more slowly as the adult ages (ref. 11).

The partially demineralized skeletal frame, having acquired osteoporosis secondary to diminished mechanical demands, will have to be reconstituted through graded exercise, dietary or parenteral calcium, magnesium, phosphorus and fluoride containing salts, and amino acids and vitamins. The older the skeleton's host, the less rapid is the remineralization of the bone.

Julius Wolff, in 1868, made an observation which has become known as Wolff's Law (ref. 13). This states that "Every change in the form and the function of bones, or in their function alone, is followed by certain definite changes in their internal architecture, and equally definite changes in their external conformation, in accordance with mathematical laws." This law will have remodeled the entire supporting

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skeletal frame of the space traveler, and weeks to many months will be required to reform the skeleton as an effective operational 1-g structure.

It must be remembered that many of the joints must work with micrometer precision, particularly those in the foot and ankle. The space travel remodeling of the skeleton will have produced certain alterations in the joint faces, and if a sudden and sustained imposition of 1-g is brought to bear for too long upon the remodeled joints, irreparable damage will occur. Many joints are foci for pressures of several hundred pounds when quick motions or moderately heavy lifting is carried out (especially those in the ankle, knee, hip, lumbar spine, and pectoral girdle).

Rehabilitating and reconditioning the older person to 1-g will prove more time consuming than will be the case with the younger person. All persons will experience some muscle atrophy in environments having a gravitational force of less than 1-g (ref. 6). However, it should be emphasized that a great deal of individual variation on this matter will exist. The older person who initiated his space voyage in good physical condition from the athletic standpoint, and who has a life history of maintaining reasonably good physical condition, will be a better candidate for terrestrial rehabilitation. Fat tissue should be kept at a minimum during the space voyage, and some type of spring exerciser should be employed for all major muscle groups during the trip.

Tied in with the individual variation matter, is the factor of genetic endowment, wherein some older persons will simply have constitutions which provide what can be called, for want of a better term, good "tissue vitality."

The ligaments and tendons will become somewhat attenuated under diminished gravity. There will be a tendency for the subluxation of certain joints following return to Earth, particularly in older persons if stressful physical activity is undertaken too soon.

Joint cartilage shows some degree of irreversible wear and tear in most older persons. Therefore, the older cosmonaut, upon return to 1-g conditions, must receive special attention relative to the reconstitution of his cartilage. Adequate time must be allowed for the synovial membranes to respond to the increased demands placed upon them for joint lubrication. Perhaps information on this factor, and other factors, may be obtained by extrapolation, through studies of animals shifted for prolonged periods to environments where more than 1-g force prevails (ref. 21).

Inherent in all of these musculoskeletal connective tissue readjustments, is the matter of tissue nutrition. Shut-down capillary and lymphatic bed segments will have to be reopened. The endothelium of long-dormant micro-vessels will have to be revitalized. Of special significance here, is the myocardium, which will very likely have developed a degree of atrophy secondary to the reduced demands under near-weightless conditions. A similar atrophy of the postural muscles will lead, shortly after return to Earth, to malaise and general fatigue, until adequate reconditioning has occurred. This will be particularly bothersome for older persons.

The reactivation of capillary and lymphatic beds in atrophic muscles will be complicated by the aging process, which, in some as yet ill-defined fashion, diminishes the vascular system's capability in this regard. Furthermore, chronic exposure to low levels of ionizing radiation, a certainty of prolonged space travel, produces distinct irreversible damage to vascular endothelium (refs. 1, 15, 16).

With regard to the neurophysiologic and psychologic aspects, the middle-aged and older individual, by and large, will have the advantage of a diminished desire for sexual activity. Furthermore, since most of the persons over 45 have completed their procreational roles, the risk of passing any radiation-induced genetic defects to future generations is markedly diminished. For the post-menopausal female space traveler, menstruation will be no hygienic problem, and no hormonal preparations for the suppression of menstrual flow will be necessary (menstruation could lead to excessive iron loss on prolonged trips, a matter which must be given careful consideration).

In general, an increased tolerance of monotony accompanies aging (ref. 14). Older persons are more frequently better suited to prolonged tasks which involve routine manipulations (ref. 20). The older person may prove to be better able to withstand sensory deprivation. Cultural and personality factors play a role here, of course. We must await space simulator studies before we can pull this information together relative to space travel (ref. 6).

It has been observed in industry that older persons tend to place an increased value on the precision of performance, rather than on the speed of performance (ref. 2). This certainly has implications bearing upon the quality of a given task.

On the negative side, the older person is less tolerant of "time-pressure" tasks, particularly if such tasks are relatively new to him. Furthermore, by virtue of having had longer experience in general, more alternative solutions to a given new problem are apt to occur to the older person, with the result that he suffers a "time-lag" in deciding upon which of the several possible solutions is preferable.

The presbyopic eye, with its far out "near-point," is a distinct disadvantage to the older cosmonaut who must move in confined quarters. This and other factors have been assessed for driving and flying (refs. 7, 10). Shock-resistant spectacles with hardened plastic lenses will be a must. On the other hand, the older eye, with its physiologically yellowed lens, is less susceptible to dazzle under conditions where blue or green light predominates (ref. 8).

Up to the mid-sixty age range, in the context of this paper, hearing, graviceptor sense (ref. 17), and other neurophysiologic functions, including reaction time, should not have changed enough through aging to interfere with the functions of the non-pilot members of the space crew.

From the group dynamics standpoint, relative to small groups undertaking prolonged missions under conditions of extreme group isolation, the older person can exert a distinct stabilizing effect upon the group as a whole. The older person's past history and longer occupational experience (ref. 3) provide an opportunity for a more complete assessment of the manner in which he, as an individual, handles his aggressive and hostile feelings. His reactions to emergencies and his particular emotional outlets can be more fully estimated.

Little has been said here of pathology. Clinical coronary artery disease is most frequently first discovered in the fourth to sixth decades. It can be anticipated that within the next five years, the sufficiency of coronary blood flow and myocardial irrigation following each heart beat will be a matter readily determined in a given individual on an outpatient basis. The test will possibly involve the use of a bolus of fluid containing radioactive material. Also, perhaps within the next decade, an immunologic test for covert neoplastic conditions will be perfected.

The above discussion covers a broad spectrum of considerations in the field of aging. As of January 1961, the National Institutes of Health was supporting 700 research grant projects in the field of aging, ranging from studies of the biologic aspects, through disease processes, to behavioral aspects (ref. 22). In addition, 100 intramural research projects in aging were under way at NIH during 1960. These 800 projects are supported at a level in excess of 16 billion dollars. It can be anticipated that certain of these projects will develop information pertinent to space medicine.

A final point here, with regard to time dilatation and space travel, is that although a certain slowing of the biologic clock apparently can be expected at higher velocities (ref. 9), the greater velocities, if sustained over longer distances, will necessarily entail an increased exposure to ionizing radiation. The effectiveness of the shielding will become attenuated, and it is quite possible that the gains in longevity through time dilatation will be more than offset by the tissue damage caused by the radiation (ref. 5).

SUMMARY

Sooner or later, in the evolution of space travel, persons in the fifth and sixth decades of life will desire to be part of the non-pilot space crew. It is clear that the progressive changes due to the aging process will require special consideration when the older space traveler returns and undergoes terrestrial rehabilitation.

Following a space voyage, skeletal elements, particularly the bone and cartilage of the weight bearing parts of the skeleton, must be remodeled according to Wolff's Law. The myofibrils of muscle must be reduplicated many times over, and dormant capillary beds must be reactivated.

In general, it can be said that certain assets are brought by the older person to the realm of space flight. These include a greater tolerance of monotony and repetitious manipulations, and a longer history of performance under different conditions.

Additional parameters relative to the aging person and space flight are delineated, including the cardiovascular system, the reproductive system, ionizing radiation, and time dilatation.

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APPENDIX D

AEROSPACE GERONTOLOGY*

Alex Comfort

One consequence of the U.S. NASA shuttle program is that two additional disciplines — gerontology and geriatrics, the study of fundamental aging mechanisms with a view to their control, and the medicine of later life — have become highly relevant to aerospace medicine.

The occasion for introducing geriatrics into aerospace medicine is practical. As long as crew selection for space flight was confined to fully trained professional astronauts and involved exceptionally arduous requirements, space physiology was limited to the responses of the young fit adult. The shuttle program, however, gives the facility to fly passengers, including specially qualified older persons — senior scientists and technicians. This change in selection criteria makes it essential to examine response to acceleration, weightlessness, and re-entry over the whole adult lifespan, not only its second quartile. The practical and immediate aim is to avoid hazard to passengers and the need for emergency return to Earth. But, because medicine has never been able to undertake it on the scale or with the resources now needed to establish flight criteria, the fundamental study of unconventional stress response at higher ages has great potential value for geriatrics in the nonflight context.

One example of the probable spinoff is already evident: It has long been clinically known that bed rest is increasingly deleterious to patients as they grow older, but only when bed rest was studied operationally (Donaldson et al., 1970; Miller et al., 1965) as a model of weightlessness were systematic studies of its physiological effects made available on a large scale. The establishment of flight criteria, as they will be based on performance tests, not arbitrary age qualifications, also promises to contribute to a key practical problem of both geriatrics and gerontology, the nonactuarial estimation of biologic age (Comfort, 1972). Another innovative area is the investigation of system trainability in the control of response at high ages, which has novel therapeutic possibilities. While geriatricians have exertise to contribute to the special problem of flying older persons, aerospace — with its excellent physiological resources — has the potential to contribute large medical benefits to the medicine of later life in the course of addressing its own agenda.

GERIATRIC ASPECTS

The classic pattern of change in physiologic response with age is that observed by Verzár in relation to cold adaptation (Verzár, 1963). Response becomes later and in some systems lower overall, though delay is more prominent than deficiency, as in the case of enzyme-inductive processes where one system component is located in the hypothalamic system (Adelman, 1975). Pathologies also accumulate with age, and variance in most parameters increases in both man and rodents (Storer, 1965), so that

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individual assessment becomes mandatory — where variance appears to decline, this is usually because responsive reserve is decreased and the old organism is living close to maximal response. Thus, further loading may cause system failure rather than mobilization of reserve capacity.

Besides these more general characters of older organisms, a number of physiological areas in normal aging can be pinpointed as likely to be exacerbated by weightlessness, particularly calcium loss from bones and muscular atrophy. On the other hand, the point at which trouble is most likely for the older fit passenger is not during the weightless state but in readapting to gravity on return to Earth, at which time effects such as joint pains, vestibular disorientation, and "labor" with voluntary movements (Gibson, 1977) as well as other phenomena which are minor in younger crew [gravitational purpura, for example (Hordinsky, 1977)] may last longer, or be more severe, or both, in older subjects. During readaptation, old subjects may require, for example, protection by gravity suits which are unnecessary in young subjects. Side-effects may occur after brief exposure to weightlessness which are characteristic of far longer exposure in the young, which do not occur in the young at all, or which resolve far more rapidly in the young. If not guarded against, some such effects — for example, on joints — may trigger prolonged disability. Some of these problems can be foreseen from the model of bed rest and others from basic geriatric experience, but all need to be explored now.

FUNDAMENTAL GERONTOLOGY

The fundamental elucidation of aging mechanisms has an interest in space research which arises primarily from the possibilities of using weightlessness in one of its critical experiments.

The present model of aging is that, although a number of ongoing age processes continue to be identified in cells, organs, and molecules at the subcellular level, "universal" and simplistic pictures of aging attributing it to a single local change fail to explain the phenomenon of lifespan. Similar animals (sheep and goats, Mus and Peromyscus) may differ radically in lifespan; moreover, the rate of aging has long been known to be easily modified by simple general interventions such as caloric restriction. We have already discussed the possibility that the actual, observed lifespan, which has every appearance of being an evolutionarily programmed rather than a purely statistical phenomenon, is timed by a "clock" or "clocks" in the hypothalamus coupled to metabolism, which may also be responsible for fixing the reproductive rate and the rate of development, quantities that must for population-dynamic reasons be integrated with species longevity.

One result of the model is that weightlessness, which cannot be produced on Earth, and hypergravity, which can, become attractive tools for the analysis of the weight-metabolism-longevity loop. The question is not whether the body has a direct mode of baroception — in the case of bone or of cardiac load it clearly has — but whether the integrative "clock" has one; and whether the hypothalamus, which is chiefly a chemical sensor, reads body weight as an index of instantaneous body mass, either directly or by a second-order derivate from proprioception. If it does, then changing g can be used to dissect the inputs to the "clock" or to identify some of its outputs in oligopeptide hormones. If it does not, altered g will create an unconventional discrepancy between the clock and general homeostasis, which is partly baroceptive and responds to mechanical loading, for example, of the heart and muscles, with potentially instructive results.

The analysis of the hypothetical "clock" is important to clinical gerontology because it cannot easily be attacked by direct calorie restriction in man. Human application depends clearly on analysis of how dietary restriction operates, with large possibilities for much simpler intervention if this can be done. Critical to this analysis is an understanding of precisely how the "clock" compares caloric intake with growth and body mass. An example of this aspect of the clock can be seen in the coupling of menarche to body weight, and of the continuance of menstruation to projected weight-for-age (Frisch, 1973).

Such short-term analytic experiments designed to settle specific problems have attractions as part of the shuttle program. Study of appetite, caloric intake and balance, circadian rhythms, and neurohormonal levels in brain and organs — especially somatotrophin, somatostatin, and prolactin might be used to investigate the transduction of "size" to the neurohormonal clock within the 7-day limit of early projected shuttle flights. Because most hormone levels in the brain are likely to be disturbed by re-entry, they could not be reliably done on recovered animals. Experiments might be performed at hypergravity in centrifuge studies such as those of Oyama (Oyama and Platt, 1965), but these, for the reason given above, really call for a ground-based centrifuge facility designed to allow material such as brain to be collected at steady state without stopping the centrifuge. Apart from difficulty of manipulation, this method might well prove more expensive than the use of the shuttle.

The development of Cosmos and Skylab indicates that lifetime mammal studies will eventually be able to be conducted under weightlessness, but there is no a priori reason to forecast either major changes in lifespan in adapted rats, or the sign of any changes that occur. To be significant in gerontology, serendipity would have to give a prolongation of lifespan in weightlessness. The life of rats can be shortened by nonspecific assaults of all kinds; only gross prolongation over Earth findings would be of interest, and there is no reason to expect this. The time has passed for shotgun experiments based on the idea that because weightless conditions are available they should be tried, on age-related as well as on other processes, to see what if anything happens. More important is the recognition of a) key specific experiments, like the analysis of size-proprioception; and b) extension of other nongerontological types of experiment, human and animal, to include high-age groups as well as young adults, so that a complete age spectrum of process becomes available.

The data derived from all experiments in aerospace physiology should also be scrutinized with gerontology in mind. As an example of the spinoff from such monitoring, most easily conducted when a gerontologist is included in the flight task forces, is the fact that much theory has been devoted to the crosslinking of collagen as a mechanism of aging or as an index of physiologic age. In recent flight experiments, it has been found that weightlessness appears from urinary amino-acid levels to mobilize pre-formed collagen (Leach and Rambaut, 1977). Thus, contractility and fluorescence estimates of collagen age on weightless animals become well worth making, for an object unconnected with ordinary aerospace physiology but one very interesting to experimental gerontologists. Clearly, findings of similar interest can be expected, or could be secured if protocols were run by a gerontologist in the course of preparation for other kinds of experiment.

PLANNING

The main points in a program of aerospace gerontology and geriatrics can be listed as follows: its mission would be to apply geriatric knowledge to aerospace

problems and aerospace capacity to specific, clearcut, gerontological problems in short-term experiments, and the presence of geriatric and gerontological investigators in the aerospace establishment should be used to ensure a two-way flow of information from and to the clinical and research areas of these subjects. Definite areas of study should include

1. Determination of flight criteria for ages greater than 50 years.

2. Physiological research on effects of acceleration, weightlessness, and other relevant factors in humans and animals throughout life, not only in young adults.

3. Study of individual variation and the development of nonactuarial measures of homeostasis and "physiologic age" — in the first place for crew selection, but with a constant eye on general clinical, actuarial, and other applications.

4. Investigation of specific changes such as bone Ca loss which mimic those of aging and may be exacerbated by it; measures to limit loss in weightlessness might provide protection against senile osteoporosis, and so on.

5. Study of readaptation of older subjects to re-entry, with a precautionary emphasis, and of control of adverse reactions by training.

6. Specific flight and ground experiments aimed at defined questions, such as the analysis of the lifespan "clock."

7. Gerontological and geriatric presence in aerospace programs to identify problems and unrecognized sources of information.

These objects alone are more than sufficient to establish the reality of "aerospace gerontology" as a necessary area of interest and to ensure the harvesting of valuable data from missions in hand.

APPENDIX E

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16 Abstract

A workshop on Space Gerontology was held at Ames Research Center on January 30-31, 1978. Workshop chairman: Alex Comfort, M.B., D.Sc., Institute for Higher Studies, Santa Barbara, Calif., and Neuropsychiatric Institute, U.C.L.A., Los Angeles, Calif.

These proceedings contain the scientific communications presented at the workshop as well as the edited transcript of the discussions.

The main goal of the workshop was to initiate an exchange of views between NASA space biologists and physiologists concerned with the effects of weightlessness and experimental gerontologists from universities and research institutes, whose main interest is understanding the aging process. Accordingly, the proceedings deal with the previous research of the participants on animals and humans exposed to abnormal gravitational loads in centrifuges and on board space vehicles. The results of these NASA studies are discussed from the viewpoint of their possible contribution to elucidating the mechanisms of cell and organismic aging in normal and abnormal environments.

The proceedings also include a preliminary discussion of gerontological experiments worth performing on board the Shuttle and a number of speculations by several participants on the probable effects of long-term exposure to weightlessness on the passengers and crews of space vehicles.

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